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Role of islet peptides in beta cell regulation and type 2 diabetes therapy

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ABSTRACT

The endocrine pancreas is composed of islets of Langerhans, which secrete a variety of peptide hormones critical for the maintenance of glucose homeostasis. Insulin is the primary regulator of glucose and its secretion from beta-cells is tightly regulated in response to physiological demands. Direct cell–cell communication within islets is essential for glucose-induced insulin secretion. Emerging data suggest that islet connectivity is also important in the regulating the release of other islet hormones including glucagon and somatostatin. Autocrine and paracrine signals exerted by secreted peptides within the islet also play a key role. A great deal of attention has focused on classical islet peptides, namely insulin, glucagon and somatostatin. Recently, it has become clear that islets also synthesise and secrete a range of non-classical peptides, which regulate beta-cell function and insulin release. The current review summarises the roles of islet cell connectivity and islet peptide-driven autocrine and paracrine signalling in beta-cell function and survival. The potential to harness the paracrine effects of non-classical islet peptides for the treatment of type 2 diabetes is also briefly discussed.

1. Endocrine pancreas (Islets of langerhans)

The islets of Langerhans are richly innervated clusters of cells scattered throughout the pancreas that play a vital role in glucose homeostasis. A great deal of research in recent decades has focused on the anatomy of the islets, the interactions of cells within the islets and the expression and secretion of different islet peptides. Islets are primarily composed of five heterogeneous types of cells: alpha, beta, delta, PP and rarely found epsilon cells. These cells produce glucagon, insulin, somatostatin, pancreatic polypeptide and ghrelin respectively. Table 1 summarises the primary islet cell types and their effects on insulin and glucagon secretion. A normal adult human pancreas comprises about 1,000.000 islets distributed irregularly and constitutes approximately 2% of total pancreatic mass [1]. Islet morphology differs from rodent to human. In rodent islets, beta-cells (60%–75%) cover the core surrounded at the periphery by alpha cells (20%), with delta cells (3–5%) and PP cells (F cells; 1–2%). In contrast, in humans, alpha cells are distributed throughout the pancreatic islets [2]. The autonomic nervous system controls endocrine pancreatic secretions and constitutes an integral part of regulatory system of the islets [3]. Similar to islet cell distribution, the nerve innervation pattern differs in human and rodent, yet the impact of neuronal control of hormone secretion is comparable in both the species [4]. Pancreatic islets are highly vascularized and are innervated by both sympathetic and parasympathetic nerves. The parasympathetic nerves stimulate the release of both insulin and glucagon whereas sympathetic system stimulates glucagon secretion whilst inhibiting insulin secretion [5].

The endocrine cells within the islets interact with each other via both paracrine and autocrine mechanisms to maintain glucose homeostasis in the body [6] as shown in Fig. 1. Beta-cell function and the regulation of insulin secretion in particular, is regulated by a complex set of interacting factors including autocrine and paracrine singalling, cell–cell communication, and neuronal, cellular and vascular regulation [7]. The current review summarises the roles of cell–cell interactions and autocrine/paracrine signals conferred by peptides released from within the islet on beta-cell function and glucose homeostasis. The potential to harness the paracrine effects of non-classical islet peptides for the treatment of type 2 diabetes is also briefly discussed.

2. Cell-cell interactions in the regulation of beta-cell function

Cellular communication between somatic cells is largely facilitated by gap junction channels [8]. These channels are formed by the apposition of two transmembrane structures called connexons. Each connexon comprises six connexins containing both C- and N-termini in the cytoplasm, a cytoplasmic loop and two extracellular loops [9]. The

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Table 1
Major secretory products of islet cells and their associated physiological roles. Pancreatic islets comprise 5 major cells types that secrete glucagon (alpha-cells), insulin (beta-cells), somatostatin (delta-cells), polypeptide (PP cells) and ghrelin (epsilon cells). Islet hormones act to exert a variety of physiological roles with the ultimate aim of establishing glucose homeostasis. Green arrows indicate a stimulatory effect, while red arrows indicate an inhibitory effect on hormone release (For interpretation of the references to colour in this Table legend, the reader is referred to the web version of this article).

Peptide	Secretion	Effect on insulin secretion	Effect on glucagon secretion	Effect on somatostatin secretion	Role
Glucagon	Alpha	↑	-	↑	Secreted in response to low glucose, promotes gluconeogenesis, and glycogenolysis
Insulin	Beta	-	↓	-	Secreted in response to high glucose which aids in uptake of glucose in body cells
Somatostatin	Delta	↓	↓	-	Inhibits secretion of hormones including insulin, glucagon, gastrin, somatotropin and thyrotropin
Pancreatic polypeptide	PP (F cells)	↓	↓	↓	Inhibition of exocrine secretion in pancreas and gall bladder motility
Ghrelin	Epsilon	↓?	↑	↓	Function uncertain, but may promote local cell growth and maturation and regulation of insulin secretion

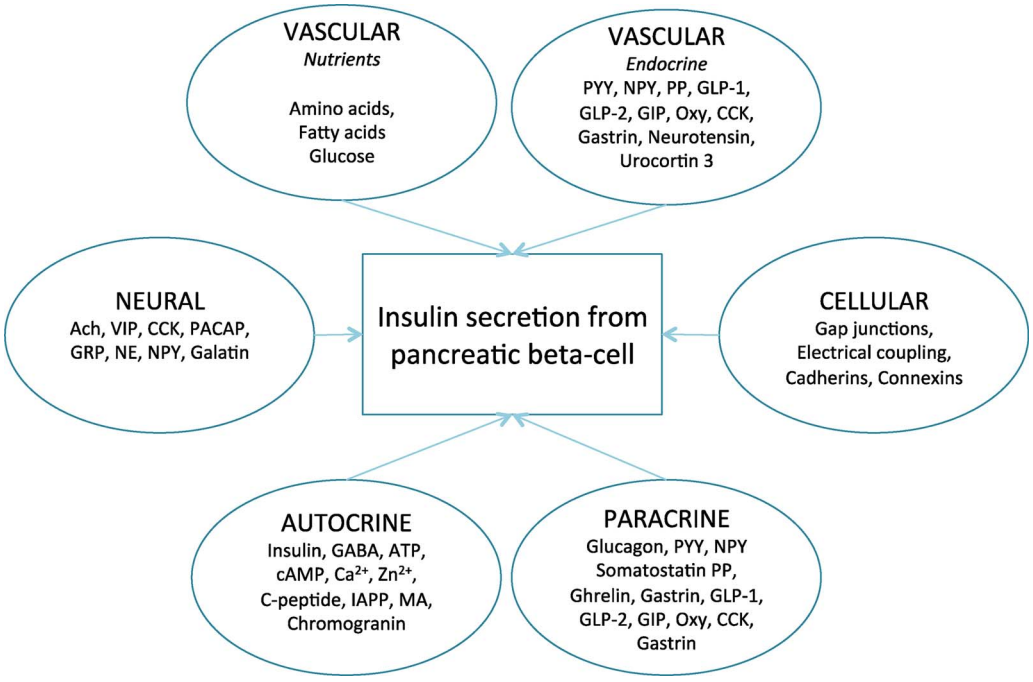

Fig. 1. Factors influencing beta-cell function and insulin secretion. Regulation of insulin secretion involves integration of signals derived from many pathways including autocrine, paracrine, neural, vascular and cellular pathways. The examples provided in the Figure, do not exclude the potential involvement of less-well studied regulators. Ach, acetylcholine; CCK, cholecystokinin; GABA, gamma aminobutyric acid; GIP, glucose-inhibitory polypeptide or glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; IAPP, islet amyloid polypeptide; MA, monoamines; NE, norepephrine; NPY, neuropeptide Y; Oxm, oxyntomodulin; PACAP, pituitary adenylate cyclase-activating polypeptide; PYY, Peptide YY; VIP, vasoactive intestinal polypeptide.

connexon of one cell will dock with the connexon of an adjacent cell to create a channel through which molecules of less than 1 kDa may directly pass [10]. The correct alignment of one connexon with the connexon of a neighbouring cell is achieved through a family of glycoproteins called cell adhesion molecules (see [7]). Numerous classes of cell adhesion molecule exist including the selectins, integrins and cell adhesion molecules (CAMs) themselves [11]. However, in the pancreatic beta-cell at least, the calcium-dependent cadherin family has been credited with creating and maintaining gap junction channels between adjoining beta-cells [12].

Several forms of cadherin exist: placental-cadherin (P-cadherin), neural cadherin (N-cadherin) and epithelial cadherin (E-cadherin) – found in notable quantities in the beta-cell [13]. Furthermore, E-cadherin is thought to play a significant role in the maintenance of islet ultrastructure since a loss of E-cadherin expression has been associated with altered islet morphology [7,14,15]. It is entirely possible for islet-