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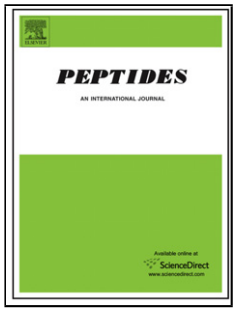

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Classical and non-classical islet peptides in the control of β-cell function

Running title: Peptides controlling β-cells

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Highlights

- Islets of Langerhans are comprised of various cell types whose primary function is producing hormones involved in blood glucose control and the regulation of nutrient metabolism.
- Enteroendocrine cells present in the intestine produce a wide variety of peptide hormones which regulate islet function and metabolism.
- Many of these gut peptides are also produced in islets, thereby impacting glucose sensing and insulin secretion as well as proliferation, survival and transdifferentiation of islet cells.

Abstract

The dual role of the pancreas as both an endocrine and exocrine gland is vital for food digestion and control of nutrient metabolism. The exocrine pancreas secretes enzymes into the small intestine aiding digestion of sugars and fats, whereas the endocrine pancreas secretes a cocktail of hormones into the blood, which is responsible for blood glucose control and regulation of carbohydrate, protein and fat metabolism. Classical islet hormones, insulin, glucagon, pancreatic polypeptide and somatostatin, interact in an autocrine and paracrine manner, to fine-tube the islet function and insulin secretion to the needs of the body. Recently pancreatic islets have been reported to express a number of non-classical peptide hormones involved in metabolic signalling, whose major production site was believed to reside outside pancreas, e.g. in the small intestine. We highlight the key non-classical islet peptides, and consider their involvement, together with established islet hormones, in regulation of stimulus-secretion coupling as well as proliferation, survival and transdifferentiation of β-cells. We furthermore focus on the paracrine interaction between classical and non-classical islet hormones in the maintenance of β-cell function. Understanding the functional relationships between these islet peptides might help to develop novel, more efficient treatments for diabetes and related metabolic disorders.

Abbreviations

CCK, cholecystokinin; CNS, central nervous system; EEC, enteroendocrine cells; FFA, free fatty acid; GIP, glucose dependent insulinotropic peptide; GLP, glucagon-like peptide; PYY,

Peptide Tyrosine Tyrosine; PP, Pancreatic polypeptide; NPY, neuropeptide Y; GABA, γ-aminobutyric acid.

Keywords: Islet, β-cell, insulin secretion, transdifferentiation, autocrine, paracrine.

Introduction

Herophilus of Chalcedon, often known as the father of anatomy, first recognised the pancreas as an organ approximately 2000 years ago [1]. Claude Bernard's work on pancreatic juice and digestion solved the mystery of the physiological role of the pancreas leading to rapid acceleration of research in this area [2]. In 1869, Paul Langerhans, a medical student, discovered clusters of cells within pancreas which later were named islets of Langerhans [3]. Human pancreas harbours between 3.2 and 14.8 million islets [4, 5], each functioning as a micro-organ with its own vasculature, innervation and complement of different hormone-producing cells. Islets are comprised of five main secretory cell types: most populous (60%) insulin-secreting β-cells, α-cells that secrete glucagon (30%), somatostatin secreting δ-cells (10%), γ-cells (also referred as PP-cells, <1%) that produce pancreatic polypeptide and ϵ-cells (trace number) that secrete ghrelin [6, 7].

It was the major role of the classical islet hormones, insulin, glucagon and somatostatin, in the glucose homeostasis that inspired several generations of diabetes researchers in their efforts to dissect the mechanisms of islet glucose sensing. These efforts suggested that, apart from their intrinsic glucose-sensing machinery, islets utilise signals from other sources such as enteroendocrine (EE) cells. Residents of the small intestine, these cells secrete a wide variety of peptide hormones in a glucose-dependent manner, which significantly assist glucose handling by the body [8]. These include but are not limited to gastric inhibitory peptide (**GIP**),

glucagon-like peptide-1 (**GLP-1**), **ghrelin**, oxyntomodulin (**Oxm**), Peptide YY (**PYY**), cholecystokinin (**CCK**), **xenin** and **gastrin**. Remarkably, the small intestine is the main but not the exclusive site to produce these gut peptides. Various islet cell populations have been reported among the multiple auxiliary sources of the peptides above, which won the latter a reputation of non-classical islet peptides [9-11]. A perfect example of a peptide first isolated from extra-pancreatic tissues, which is now recognised as an islet hormone, is ghrelin. The non-classical islet peptides can thereby exert important intra-islet effects on β-cell function, thus representing potential target(s) for the treatment of type 2 diabetes.

Below, we focus on recent advances in our understanding of the role of classical and non-classical islet peptides and their contribution to the regulation of β-cell function and fate. The progress in this vibrantly developing field [12] is hoped to result in improved therapeutic approaches to diabetes and related disorders, thereby improving patient care.

Islet Architecture: rodent vs human

The unique cellular organisation of pancreatic islet adapts to metabolically demanding situations, such as pregnancy and obesity, to maintain glucose homeostasis. [13]. A dense intra-islet vascular network [14] as well as presence of autonomic nerve fibres [15] and immune

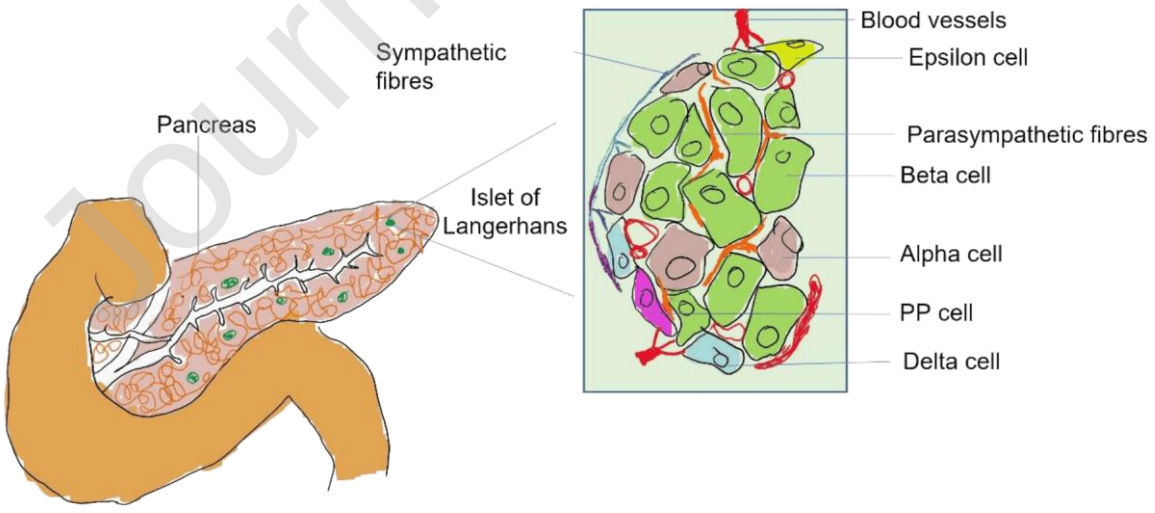

Figure 1: Islet architecture sketched, with different cell types and vessels.

cells [16] contribute to a well-orchestrated endocrine signalling mini-organ, functionally fine-tuned by autocrine and paracrine interactions.

The dominating population of β-cells is tightly coupled electrically in 30-40 cell clusters [17, 18], via connexin-36 gap junctions [19], thereby guaranteeing a strong collective all-or-nothing response to metabolic stimulus. Likewise, frequently clustered, appear α- and δ-cells [20], possibly due to the developmental reasons. Vital for supplying islet cells with oxygen and metabolic nutrients, the inter-islet vasculature is at the same time a critical avenue for conveyance of locally secreted peptides to their intra-islet targets [21]. The density of the vascular network was found to correlate positively with islet glucose sensing ability [22] and proliferation of islet cells [23].

The rodent islet arrangement is straightforward (**Figure**); however, morphological analysis of human islets suggest a more complex intermingling of islet cell types. Whilst earlier studies reported close similarity to the rodent counterparts as for the α- and β-cell content but with more heterotypic cell contacts [7], recent works revealed a substantially higher proportion of α-cells within the human islets [24], with a greater percentage of β-β-cells contacts [25-27]. The capacity for β-cell proliferation is low for adult human islets [28], therefore the heterotypic cell arrangements within human islets are believed to set at the early stage of development [29, 30]. Likewise, the vascular network has been reported to be much denser in mouse islets [31], possibly due to the age-dependent degradation of inter-islet vasculature, induced by the inflammation and fibrosis, likely leading to dysfunction of islets within the ageing human body [32].

Islet hormones

Classical islet peptides and their function

The overwhelming majority of islet studies to date have focused on β-cell function, although these multi-faceted micro-organs are more than just insulin-producing factories. The body's

only hypoglycaemic hormone, **insulin** is derived from a precursor proinsulin, via an enzymatic cleavage, yielding equimolar amounts of insulin and C-peptide. Whereas the primary function of insulin in humans is to regulate the sequestering of the elevated plasma glucose into liver, muscle and adipose tissue, the function of C-peptide within the body is still a matter of speculation [33]. Beyond debate is the utilitarian role of this mysterious post-translational proinsulin product, which has been successfully used as a surrogate to report the portal levels of its 'non-identical twin' insulin, - an otherwise very challenging task, given high rates of clearance for insulin by peripheral tissues, such as liver [34, 35].

Apart from its role in glucose homeostasis, insulin regulates lipid uptake, synthesis, reduces the lipolysis [36] and promotes protein synthesis [37]. At the same time, insulin secretion by β-cells is triggered almost exclusively by elevations in plasma glucose and gets enhanced by other nutrients, incretin hormones, parasympathetic nervous stimulation and several regulatory peptides [38]. In contrast, factors like somatostatin, epinephrine, galanin, ghrelin, and leptin inhibit insulin secretion [38, 39].

α-Cells produce the hyperglycaemic hormone **glucagon**, which is derived from a larger proglucagon precursor molecule. Interestingly, the latter is expressed in many tissues within the body but gets processed in different, tissue-specific ways, yielding a variety of peptide products [40]. Glucagon is secreted in response to stress [41], hypoglycaemia [42], and various hormonal stimuli [43] plus amino acids [44] circulating in the blood under fasting conditions. In turn, the inhibition of glucagon release has been attributed to insulin [45], γ-aminobutyric acid (GABA) [46] and, naturally, hyperglycaemia [47]. Glucagon predominantly targets a G_s protein-coupled receptor on hepatocytes thereby elevating cytosolic cAMP, which in turn switches glucose metabolism from utilisation to production via gluconeogenesis [48]. The cAMP signal also favours phosphorylation of the polymeric inactive form of glucose, glycogen, into monomeric glucose-1-phosphate (glycogenolysis) [49]. Additionally, glucagon

regulates uptake of amino acids [44], production of ketone bodies [50] by the liver and the breakdown of stored triglycerides into free fatty acids and glycerol in mouse but not in human models [51].

δ-Cells, constituting a substantially smaller proportion of islet endocrine cells than alpha cells, secrete a potent G_i receptor ligand **somatostatin** that reduces secretion of every pancreatic hormone, inclusive of insulin and glucagon, by decreasing the cytosolic cAMP and attenuating late events in vesicle exocytosis [52]. In this way, somatostatin may counteract large variations in circulating hormone levels [53]. Morphological analysis has shown a unique neuron-like δ-cell structure, which contributes to its effective communication with neighbouring α- and β-cells [54-56]. Principally activated by increases in plasma glucose [57], δ-cells nevertheless express receptors for insulin, GLP-1, GIP and ghrelin suggesting the importance of these local islet interactions [58] as well as plasma ionic composition [59].

A minor islet population of PP cells secrete **pancreatic polypeptide,** which is regulated by vagal and enteric nervous input [60]. Despite a substantial postprandial increase in PP [61], PP-cells do not respond well to direct action of glucose or other nutrients [62]. Historically, PP has been viewed as a principal inhibitor of exocrine pancreatic secretion [63], however it has been demonstrated to inhibit secretion of endocrine hormones, such as insulin [10, 64] and glucagon [65]. ϵ-Cells, the smallest islet cell population, produce **ghrelin** [66, 67] which is also secreted by enteroendocrine cells of the stomach [68]. The 'hunger hormone' ghrelin regulates appetite at the systemic level, in line with its intra-islet role of inhibiting insulin release [69], most likely via stimulating the release of somatostatin [66].

Non-classical islet peptides and their receptor expression in endocrine pancreas

The non-classical islet peptides are a family of regulatory peptides which are conventionally produced in extra-pancreatic sites but have been reported to be expressed in subsets of islet cells. The incretin peptide **GLP-1**, is predominantly secreted by intestinal L-cells [70] where

it is cleaved from proglucagon by the tissue-specific prohormone convertase PC1/3. The expression of GLP-1 in pancreatic α-cells, controlled by the glucagon-oriented proconvertase 2 (PC2), is low under physiological conditions but may increase under stress such as depletion of β-cells [71], associated with type 1 diabetes [72-75]. GLP-1 potentiates glucose-induces secretion of insulin, just like its 'sister' peptide, gastric inhibitory peptide (**GIP**). GIP is synthesized from the proGIP precursor, processed by PC1/3 and is secreted in a glucose-dependent manner by enteroendocrine K-cells in duodenum [76]. Historically reported as an inhibitor of gastric acid secretion, GIP exerts 'global' anabolic effects on both adipose tissue and bone [77]. The local expression of GIP within the islet, attributed to α-cells [11, 78, 79] is expected to target neighbouring β-cells as well as α-cells, in an autocrine fashion.

Another preproglucagon splicing variant, **GLP-2** is conventionally expressed in L-cells within the distal small intestine and is believed to target the intestinal mucosa. Similarly to GLP-1, GLP--2 is the product of PC1/3 processing, which has been detected to express in the islet α-cells, under the β-cell stress [80, 81]. The latter has been shown to upregulate PC1/3 expression in α-cells [71, 74, 75, 82].

Another gut peptide, **PYY** (Peptide tyrosine-tyrosine), co-localises with GLP-1 in the secretory vesicles of intestinal L-cells and is co-secreted with this incretin [83]. Two main bioactive forms of this peptide, PYY(1-36) and PYY(3-36), are believed to impact islet function [84] and appetite regulation [85], which might help convey the glucoregulatory benefits of Roux-en-Y bariatric surgery. Appreciable amounts of PYY have been detected in the islets [86] and PYY immunoreactivity has been reported in a subset of rodent α-cells [9, 87]. In our hands, PYY attenuated glucose-induced insulin secretion on the acute timescale [9].

Hypothalamic neuropeptide Y (**NPY**), a 36 amino acid peptide homologous to PYY and PP, is recognised for its role in the regulation of energy balance by central nervous system [88]. Expression of NPY in islet PP-cells and sympathetic nerve fibres of the pancreas have been

reported in rodents [10, 89]. In diabetes models, the intraislet site for NPY expression changes from PP cells to δ-cells [10, 89]. Similarly to PYY, NPY attenuates glucose-induced insulin secretion [10], but was reported to have little *in vivo* effect in humans [90].

Cholecystokinin (**CCK**) and **gastrin** are neuroendocrine peptides produced in small intestinal I-cells and gastric G-cells, respectively, whose effects are mediated through CCKA and CCKB receptor subtypes. Both CCK (CCK-8) [91-93] and gastrin [91, 92, 94] immunoreactivity have been observed in pancreatic islet α- and β-cells. Metabolic stress such as obesity [95], type 1 diabetes [91], compromised immune response [91] defective leptin signalling [96] and subsequent pancreatic regeneration serve as a putative trigger for the expression of the two peptides.

Xenin-25, co-expressed with GIP in K-cells of duodenum, and **neurotensin,** secreted by N-cells within the distal intestine and hypothalamus, are structurally related small peptides, believed to act via a common receptor [97]. Both peptides have been reported in pancreatic islets, alongside all major neurotensin receptor subtypes (NTSs) [98-100]. Xenin-25 has an acute insulinotropic effect [98], which is believed to be mediated via NTS_1 or NTS_3/sortilin; the peptide may also serve as a competitive antagonist of NTS_2 [101-103]. **Secretin**, a gut hormone that triggers flow of pancreatic juice into the duodenum, has also been reported in the islets and shown to exert acute insulinotropic effects [104].

Two small neuropeptides traditionally viewed as pituitary hormones, **vasopressin** [105] and **oxytocin** [106] have been reported in pancreatic islets with an insulinotropic as well as proliferative and antiapoptotic effect on the β-cell.

Recently, cocaine- and amphetamine-regulated transcript (CART) and apelin have been reported to express within islets. CART, a neurotransmitter and hormone, to augment insulin secretion and alter β-cell morphology [107]. The expression of apelin is upregulated by insulin

[108], whereas this adipokine inhibits insulin secretion [109]. This feedback regulation suggests a paracrine or autocrine regulatory role for apelin within the islets [110, 111].

Non-classical islet peptides regulate β-cell function

Acute effects on insulin secretion. As a highly differentiated 'professional' glucose sensor, the pancreatic β-cell couples the concentrations of the sugar in blood to the amount of secreted insulin. Glucose enters the cell via Glut2 (Glut4 [112], Glut1 or Glut3 [113], in humans) transporter and is rapidly converted into glucose-6-phosphate by low-K_d glucokinase, which is then either metabolised along the glycolytic pathway [114] or deposited in the "inactive" form, glycogen [115]. The glucose flux is strongly coupled to mitochondrial metabolism [116], resulting in a remarkably efficient (>85%) oxidation of glucose carbons [114, 117, 118]. Consequently, an increase in blood glucose is rapidly translated into a sustained elevation of ATP levels in the β-cell cytosol [119, 120]. This signal inhibits the ATP-sensitive K^+ channels [121], which depolarises the plasma membrane [122], opening voltage-gated Ca^{2+} channels. The resulting Ca^{2+} influx into the cytosol triggers insulin exocytosis. The fast, triggering, stage of insulin release is followed by a less prominent but more sustained amplification stage [123]. Whereas the former is vastly regulated by the Ca^{2+} (that initiates the vesicle fusion) and cAMP (that substantially enhances the Ca^{2+}-sensitivity of the vesicle pool) [124], the latter is shaped by a number of signals of predominantly metabolic (mitochondrial) nature [125].

The great variety of systemic signals targeting specific receptors expressed on the islet cells converges, at the intracellular level, to a very limited set of G-protein receptor-mediated signalling pathways. Glucagon, GLP-1 and GIP exert the 'incretin effect' to potentiate insulin release following feeding [126], by binding to specific **G_s** receptors (G_s α-subunit of a G-protein coupled receptor) expressed on the membrane of pancreatic β-cells thereby activating adenylyl cyclase and elevating cytosolic cAMP. At physiological concentrations, this

secondary messenger is practically unable to trigger insulin secretion *per se* [127]. It, however, substantially enhances the exocytosis triggered by Ca^{2+} [128], acting via its downstream targets, protein kinase A (PKA) [129] and Epac2 [130, 131], to enhance the Ca^{2+}-sensitivity of the intracellular vesicles. Similarly to GLP-1, GLP-2 has been reported to target a G_s receptor thereby elevating cytosolic cAMP [132], selectively in α-cells [80].

At low concentrations, GLP-1 was reported to signal via a PKC-dependent pathway to activate PKA indirectly [133], a mechanism typical for **G_q** receptor signalling that culminates in a 'bolus' release of luminal Ca^{2+} into the cytosol. G_q-mediated signalling and a rapid elevation of cytosolic Ca^{2+} are typical features of CCK- [134, 135] and gastrin-induced [136] insulin release. CCK and gastrin bind to the G_q-type CCK receptors (**CCK_1**, **CCK_2**) expressed by the islet β-cells [137]. Of note, there is no direct confirmation of the insulinotropic effects of endogenous CCK and gastrin as the studies [92, 134-136] used supraphysiological levels of exogenous peptides. Whilst the insulinotropic effects are unattainable for endogenous systemic CCK and gastrin, the local intraislet production of the two peptides may lead to the higher topical levels of CCK and gastrin within the islets.

The mechanism of the acute glucose-dependent insulinotropic effect of xenin-25 in rodent β-cells [98, 138-140] as well as indirect augmentation of PP secretion and synergism with GIP [141] is still unclear. The peptide is known to interact with NTSR **G_q** receptors [142], which is expected to induce a bolus increase of cytosolic Ca^{2+}, via the release from the luminal depot. This is however at odds with our observation of the effect on the plasma membrane potential [98], that suggests an inhibition of K+/activation of Ca^{2+} conductance. The homologue of xenin-25, neurotensin, which is expected to target a $NTSR_2$/$NTSR_3$ receptor complex [143], elevated cytosolic Ca^{2+} in INS-1E β-cells, but was in contrast reported to impose no acute effects in other systems [144].

PYY, NPY and PP bind to five known types of **Y-receptors** that are conventionally classified into the **G_i** type [145], imposing an inhibition on the target cell by attenuating the adenylyl cyclase activity and hence the cytosolic levels of cAMP. However, the acute insulinostatic effect of supraphysiological concentrations of PYY in rodents [146, 147] as well as the inhibitory effects of PYY and NPY in isolated islets and human β-cells [9, 10, 146] are putatively linked to an interference with plasma membrane electrical potential, suggesting an ion channel (such as G_{irk}) association of the peptide receptor on these cells. These inferences are however contrasted by the reports of acute [148] and chronic [149] insulinotropic effects of PYY.

Vasopressin and oxytocin receptors belong to G_q (**V_{1A}**, **V_{1B}**, **OT**) and G_s (**V_2**) types, although coupling of OT to G_i proteins has also been reported [150]. The data from a β-cell line [105, 106] demonstrating large [105] and small [106] additive effects of the phosphodiesterase inhibitor isobutylmethylxanthine for vasopressin and oxytocin, respectively, suggest an opposite pattern: the former peptide is likely to act by inducing a Ca^{2+} release from the endoplasmic reticulum whereas the latter seemingly acts by elevating cytosolic cAMP levels.

Chronic effects on β-cell biology: proliferation and survival. Diabetes mellitus is an umbrella term for several diseases of different aetiology, however increased apoptosis [151] and impaired maintenance [152] of pancreatic β-cells are common traits of different types of diabetes. The therapeutic reversal of β-cell degradation is seemingly set to rely on tissue engineering strategies, such as differentiating induced pluripotential stem (iPS) cells into new β cells [153, 154] or attenuating β-cell senescence [155], whereas one can regard the fast peptide-based signalling to be too evanescent to induce long-term effects. However therapeutic interventions aiming at prolonging the **GLP-1** receptor agonism, either by using synthetic long-lasting analogues of GLP-1 or via inhibition of GLP-1 degradation [156], reported an increase of β-cell proliferation and neogenesis as well as antiapoptotic action.

Likewise, chronic exposure to **GIP** had pro-proliferative and anti-apoptotic effects in β-cells [70, 156], supposedly mediated via the activation of CREB and suppression of both p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) [157, 158] reducing the impact of the endoplasmic reticulum stress [159]. Alongside GLP-1 and GIP, **GLP-2** has been shown to augment rodent β-cell proliferation [80] thereby echoing its role in the expansion and/or renewal of intestinal epithelium [160]. The effect on β-cells is likely to be mediated via the activity of α-cells directly targeted by GLP-2 [80].

Despite the nominally inhibitory nature of the Y-receptor agonism in β-cells, chronic exposure to **NPY** and **PYY** was shown to impose a mitogenic effect [161], thereby suggesting an involvement of Y-receptors in β-cell proliferation, similarly to their role in olfactory [162], hippocampal [163] neuronal precursors. This discrepancy, conventionally explained by 'anomalous' coupling of Y-receptors to G_q subunits [164] or an anomalous activation of PKC by the G_i subunit [165], results in an enhancement in β-cell proliferation and survival, in response to chronic PYY agonist [9, 166]. In line with the idea of G_q coupling of Y-receptors, other G_q agonists, **CCK** [167] and **gastrin** [92, 168], induced proliferation of rodent β-cells and cell lines [92, 95]. The significance of endogenous gastrin and CCK for β-cell proliferation is however challenged by the data from gastrin receptor-knockout mice that displayed unaltered islet morphology, which however might be attributable to triggering of compensatory mechanisms [169, 170].

Similarly to CCK and gastrin, another duo of chemically related G_q agonists, **xenin-25** and **neurotensin**, increased β-cell proliferation [98], presumably via NTSR3/sortlin signalling that has been reported to enhance cellular growth in other systems [171, 172].

Chronic effects on β-cell transdifferentiation. Commonly, β-cell transdifferentiation, phenotypic conversion of fully differentiated β-cells into other islet cell types, is observed under conditions of stress such as (partial) pancreatectomy, diabetes and pancreatic duct ligation [173]. Recently, we have reported that a GLP-1 receptor long-acting agonist, liraglutide, countered detrimental β- to α-cell transdifferentiation in mouse models of type 1 and type 2 diabetes [72, 174]. Likewise, chronic agonism of the islet cell GIP [175] or Y_1 [176] receptors countered streptozotocin-induced islet cell transdifferentiation and β-cell loss. Sub-chronic administration of stable analogues of xenin or oxyntomodulin (dual agonist of GLP-1 and glucagon) induced similar beneficial effects [175, 177].

Classical islet hormones	Non-classical islet hormone	Expression in endocrine pancreas	Effects on beta-cells	Receptors
1. Insulin- Inhibits glucagon	GLP-1	Alpha cells	Increase insulin secretion, beta-cell mass and transdifferentiation	GLP-1R
2. Glucagon- stimulates insulin secretion	GIP	Alpha cells	Increase insulin secretion, beta-cell proliferation and survival	GIPR
3. Somatostatin- inhibits insulin and glucagon	PYY	Alpha-, delta- and PP cells	Inhibits insulin secretion, beta-cell proliferation and survival	NPY1, NPY2, NPY4,
4. Pancreatic polypeptide- inhibits insulin	Gastrin	Alpha- and beta-cells	Insulin secretion	NPY5 CCKB R
5. Ghrelin-inhibits insulin	CCK	Alpha-, beta-cells and nerve endings	Increase insulin secretion, beta-cell proliferation and survival	CCKA R, CCKB R
	Xenin-25	Alpha- and beta-cells	GIP mediated insulin secretion, beta-cell proliferation	NTSR, Muscarinic
	Neurotensin	Exocrine pancreas, nerve	Increases basal insulin secretion, potent cellular growth factor	NTSR1, NTSR2,
	Oxytocin	endings Alpha- and beta-cells	Increases insulin secretion beta-cell proliferation and survival	NTSR3 OTR, AVPR
	Vasopressin	Alpha- and beta-cells	Increases insulin secretion, protect against cytokine-induced beta-cell apoptosis	Avpr1a, Avpr1b, Avpr2

Figure 2: Summary of classical and non-classical islet peptide expression, their receptors and effect on β-cells.

Autocrine and paracrine interactions controlling β cell function

Islet cells release a number of soluble factors of peptide (insulin, glucagon, glucagon-like peptide-1, somatostatin) and non-peptide (ATP, acetylcholine, γ-aminobutyric acid, dopamine, Zn2+) nature that have proven effects on insulin secretion [178]. Alongside insulin, the β-cell insulin vesicle contains several (poly)peptides, essential for its biogenesis such as chromogranin B and C, secretogranin 2, carboxypeptidase E, as well as VGF and islet amyloid polypeptide, which may be implicated in the autocrine regulation of glucose-induced

exocytosis [179]. The paracrine regulation of the β-cell secretory performance is accomplished in part by somatostatin, secreted by δ-cells. The main product of α-cells, glucagon is also involved in physiological regulation of insulin secretion. Apart from the two conventional molecules, the-non-β-cells express smaller amounts of a range of non-classical peptides as considered above, such as GLP-1, xenin-25, vasopressin, oxytocin or ghrelin. The proximity of these locally released peptides to the β-cells may substantially mimic or even exceed the conventional effects of these peptides produced predominantly elsewhere in the body.

Autocrine The most abundant peptide factors secreted by β-cells are the derivatives of proinsulin. Whereas the physiological role of **C-peptide** remains unclear, within islets it appears to inhibit insulin release [180]. In contrast, the abundant expression of **insulin** receptor in rodent [181] and human [182] β-cells indicates a significant role for insulin as an autocrine signal. Historically, a fast negative feedback loop was proposed for the acute (minutes) effect of insulin on β-cell insulin secretion, based on clinical observations [183, 184]. This view, however, was contrasted by mutually exclusive data from isolated islet and single β-cells [185, 186], overall suggesting a dose-dependent acute inhibitory effect of insulin on β-cells [187] and/or possible mediator role for other islet cell types [188].

There is less controversy about the long-term (days) effect of insulin on β-cell biology, as the β-cell specific knock-out of insulin receptors in a mouse model induced a type 2 diabetic phenotype [189]. Further experiments in the rodents aiming to perturb various components of the insulin-signalling pathway in β-cells suggested its critical role in the compensatory hyperplasia of islets [190, 191]. Whilst the cancellation of insulin signalling results in a clear phenotype, there is a doubt on the physiological regulation of this pathway in β-cells [192]. The saturating insulin levels within the islet vicinity *in vivo* are highly likely to desensitise the receptor [192], an observation that may explain the discrepancy with the *in vitro* findings.

Islet **amyloid** polypeptide (IAPP, amylin), a 37-amino acid polypeptide co-localising with insulin in the vesicles within β-cells [193], is released simultaneously with insulin in glucose-dependent manner at a ratio of 60:1 (insulin: amylin) [194], which however decreases to 7:1 in the circulation [195]. Amylin is believed to play a key role in the pathogenesis of Alzheimer's disease [196], however it has also been proved to target non-neural tissues such as (a subset of) β-cells [197], skeletal muscle, kidney, lung [198]. The activation of two β-cell-specific isoforms of the amylin receptor (dimers of the G-protein–coupled calcitonin receptor and receptor activity–modifying proteins 1 and 3, RAMP1, RAMP3) by supraphysiological concentrations of amylin has been reported to mildly attenuate glucose-induced insulin secretion in humans [199], whereas the inhibition of the amyloid signalling resulted in an opposite effect in human [200] and rodent [201] models. Studies in amylin knockout mice reported a perturbation of glucose handling, which was not associated with any defect in islet physiology [202]. These findings are echoed by the clinically proven reputation of amylin as a potent glucagon inhibitor, apparently utilising a non-islet mechanism for this effect [203]. Chronic (48-h) effect of amylin on β-cell biology, modelled in a cell line, was reported to depend on the rate of cell proliferation: amylin enhanced the slow (observed at low glucose) and attenuated the high proliferation rates (high glucose) [204].

Urocortin-3 (Ucn-3), a peptide hormone expressed by mature β-cells, enhances glucose-dependent release of insulin and glucagon [205]; however its potent stimulatory effect on somatostatin secretion results in overall inhibition of the islet secretory output [206]. Ucn-3 binds to corticotropin-releasing hormone receptor 2 coupled to the adenylyl cyclase, resulting in a fast elevation of cytosolic levels of cAMP [207], which however is yet to be demonstrated in pancreatic islet cells. The long-term effect of Ucn-3 on β-cell biology is unclear as it is likely to be obscured by that of somatostatin. The same lab, however, reported an upregulation of

proliferation by signalling via homologous corticotropin-releasing hormone receptor 1 [208], prompting a similar option for Ucn-3 signal.

VGF (non-acronymic) has been shown to enhance insulin secretion in glucose-dependent manner [209], by regulating the insulin vesicle maturation [210]. Significant **oxytocin** immunoreactivity has been recently reported in β-cells, with the peptide augmenting insulin secretion from primary islets and proliferation in β-cell lines [106].

Paracrine A 3.49-kDa splicing variant of the preproglucagon gene, **glucagon** is secreted by pancreatic α-cells, typically in response to low glucose [41] or increased amino acids in plasma [44]. However, the populational secretory pattern is very heterogeneous among the α-cells [211, 212]. The glucagon receptor is abundantly expressed in the neighbouring β-cells; in these cells, however the elevation of cytosolic cAMP enhances but fails to trigger insulin secretion [127]. Thus, glucagon can be viewed as a potentiator of insulin secretion under the 'borderline' conditions when the release of both hormones has been induced simultaneously.

Another splicing variant of the *GCG* (preproglucagon) gene, glucagon-like peptide -1 (**GLP-1**) is harboured by a subset of α-cells under conditions of stress such as β-cell depletion [72]. GLP-1 secretion has a recognised glucose-dependent insulinotropic action [70] and, although the lifetime of the active form of GLP-1 (7-36) is limited by the activity of the intra-islet dipeptidyl peptidase-IV, the inactive form of GLP-1 (9-36), has been claimed to elevate cytosolic cAMP, at high concentrations [213]. This suggests a potential role for both major forms of locally produced islet GLP-1. Similarly to GLP-1, small amounts of α-cell-derived **GIP** are likely to stimulate the 'borderline' insulin secretion whereas the α-cell **GLP-2** could be viewed as a stimulatory autocrine factor for α-cells. X**enin-25** and **PYY,** reported to be expressed in α-cells within mature islets, have an acute insulinotropic and insulinostatic effect, respectively [9, 87, 98], further strengthening the cross-talk between α- vs β-cells.

A ubiquitous inhibitory peptide, **somatostatin** is released from pancreatic δ-cells and triggered by glucose, alongside insulin, albeit at 1% of the insulin rate [214]. The peptide inhibits exocytosis in β- and α-cells, expressing the somatostatin receptor types 2 and 5, in rodent islets [215].

The stomach-derived 'hunger hormone' **ghrelin** is also expressed in islet ε-cells [67], which secrete the fully functional bioactive peptide [216]. Ghrelin is believed to impose a stimulatory effect mediated via an increase of cytosolic cAMP predominantly in pancreatic δ-cells [66]. Thus, the peptide is hypothesised to produce an overall inhibitory effect on insulin secretion, albeit supposedly of very limited impact due to the rarity of ε-cells in islets.

Pancreatic polypeptide (PP) and **NPY** are produced by a minor (<1%) islet population of PP-cells residing predominantly in the 'small lobe' islets, at the posterior face of the head of the pancreas [217]. Although the PP receptor (PPYR1) has been reported to reside on α-cells but not β-cells [218], the *ex vivo* studies revealed an acute inhibitory effect of exogenous PP on glucose-induced insulin secretion [10], whereas NPY is likely to act directly on the β-cell [10].

Integration of autocrine and paracrine interactions. As evident from the above, the intra-islet modulation of glucose-induced insulin secretion can be viewed as a counteraction of the insulinostatic effect of somatostatin and the insulinotropic effects of the α-cell peptides (glucagon, GLP-1, GIP, xenin-25) shaping the level of cytosolic cAMP in the β-cell. The ϵ- and PP-cell peptides are likely to provide glucose-independent fine-tuning into this variable, with PYY and GLP-2 implementing weak positive feedback on glucagon release. The ubiquitously expressed G_q agonists vasopressin, oxytocin, gastrin and CCK could provide an alternative, non-electrical, avenue for β-β cell coupling for coordinating their response to the nutrient stimulus.

Concluding remarks

In addition to the classical islet hormones (insulin, glucagon, somatostatin and PP), regulatory peptides normally associated with the gut and neurons, are present in islets and known to affect β-cell function [219]. These include glucagon-like-peptides (GLP-1, GLP-2, OXM), GIP, PYY, neurotensin, xenin-25, CCK and gastrin. Conventionally, these bioactive molecules are secreted from extra-pancreatic sites but their expression in islet lineage during embryogenesis may prove important for understanding islet growth and beta-cell proliferation.

The highly significant role of islet-derived peptides in β-cell regulation mediated via autocrine and paracrine mechanisms (summarised in **Figure** , Table 1) remains poorly appreciated. Manipulation of receptor-ligand interactions mediated locally by these peptides in islets might open new avenues for promoting β-cell function, protecting insulin-producing cells and restoring β -cell mass in diabetes.

Competing interests

The authors have no conflicts to declare.

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Table 1 Classical and non-classical islet peptides and their positive or negative effects on pancreatic β-cells.

Peptide	**Origin within the islet**	**Islet content, ng/mg**	**Systemic levels, -log(pM)**	**Principal agonist in islets**	**Effect on β-cells**	
					Insulin secretion (fast)	Proliferative/antiapoptotic (chronic)
Insulin	β-cell	100 [220]	10 - 8.7 [220, 221]	Plasma glucose	Inhibits	Compensatory hyperplasia
Amylin	β-cell	0.5 [222]	11 - 10.7 [223]	Plasma glucose	Unclear	Unclear
C-peptide	β-cell	high	9.7 – 8.4 [221]	Plasma glucose	Inhibits	Unclear
Glucagon	α-cell	high	10.7 [221]	Plasma glucose Amino acids	Stimulates	Stimulates
Somatostatin	δ-cell	high	11 [221]	Plasma glucose	Inhibits	
Oxytocin	β-cell	low	11.5 [224] – 9.5 [225]	Plasma glucose?	Stimulates	Stimulates
Gastrin	β-cell	low	10.3 [221]	Plasma glucose?	Stimulates	Unclear
CCK	β-cell	low	11.2 [226]	Plasma glucose?	Stimulates	Stimulates
Urocortin3	β-cell	0.002 [206]	10.3 [227] – 8.5 [228]	Plasma glucose	Stimulates	Unclear
VGF	β-cell	very low	11.2 – 10.4 [229]	Plasma glucose [209]	Stimulates [210]	Unclear
GLP-1	α-cell	low	10.7 [133]	Plasma glucose?	Stimulates	Stimulates
PYY	α-cell	low	11 [230]	Plasma glucose?	Inhibits	Stimulates
PP	pp-cell	low	10.6 [231]	Unclear	Inhibits	
Ghrelin	ϵ-cell	low	10.15 – 9.5 [232]	Plasma glucose?	Inhibits	
Xenin-25	unclear	low	9.8 [233]	Plasma glucose?	Stimulates	
Vasopressin	Perivascular cells [105]	low	11.3 [234]	Plasma glucose?	Stimulates	Stimulates