Published in final edited form as:

Nat Rev Endocrinol. 2018 July ; 14(7): 404–414. doi:10.1038/s41574-018-0020-6.

The somatostatin-secreting pancreatic δ -cell in health and disease

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Abstract

The somatostatin-secreting δ -cells comprise ~5% of the cells of the pancreatic islets. The δ -cells have complex morphology and may, via cellular process, interact with many more islet cells than suggested by their low number. δ -cells are equipped with ATP-sensitive potassium channels (K_{ATP} channels). These channels are open at low glucose, but close in response to glucose stimulation. This results in membrane depolarisation, initiation of electrical activity, and somatostatin secretion. Glucose also stimulates somatostatin secretion by K_{ATP} channel-independent mechanisms. The Ca^{2+} signal initiated by electrical activity leads to further mobilization by intracellular Ca^{2+} stores. Factors released by neighbouring β -cells (like GABA and urocortin-3) amplify the glucose-induced effects on δ -cell electrical activity/somatostatin secretion. Somatostatin secreted from the δ -cell acts locally within the islets as a paracrine inhibitor of insulin and glucagon secretion. The effects of somatostatin are mediated by activation of somatostatin receptors that are coupled to the inhibitory G protein, which culminates in transient suppression of α - and β -cell electrical activity and exocytosis. There is evidence that somatostatin secretion is perturbed in diabetes. This may explain the loss of appropriate hypoglycaemia-induced glucagon secretion in diabetic animals, which can be mitigated by SSTR2 antagonists. Somatostatin secretion is stimulated by hypokalaemia, a well-known by-product of insulin therapy, and this effect may, via inhibition of glucagon secretion, increase the risk of hypoglycaemia in insulin-treated patients. It is proposed that somatostatin antagonists or agents that suppress somatostatin secretion should be considered as an adjunct to insulin therapy.

Competing interests

The authors declare no competing interests.

Introduction

A human pancreas contains 1–3 million pancreatic islets^{1,2}. These are complex micro-organs that consist of several types of endocrine cell that play a key role in the regulation of whole-body energy metabolism³. Whereas insulin (secreted by the β -cells) is the body's only hormone capable of lowering blood glucose, glucagon (secreted by the α -cells) is the principal plasma glucose-increasing hormone. In general, insulin and glucagon levels vary reciprocally and the insulin/glucagon ratio determines the balance between anabolism (glucose and fat storage) and catabolism (glycogen, fat breakdown and gluconeogenesis)³.

The severe metabolic disturbances associated with diabetes that culminate in hyperglycaemia result from the combination of lack of insulin and excess of glucagon^{4,5}. Most therapeutic interventions focus on insulin: they stimulate release of endogenous insulin (i.e. by administration of sulphonylureas or GLP-1 agonists), promote insulin action, or involve administration of exogenous insulin. A serious (potentially fatal) complication of insulin therapy is hypoglycaemia. It has been estimated that up to 10% of insulin-treated diabetes patients die of 'iatrogenic hypoglycaemia' (*iatros*, Greek for healer/physician)⁶.

Because of their key roles in diabetes, the α - and β -cells have been the focus of much research during the last 30–40 years. We now have a very good understanding of the regulation of insulin secretion^{7,8}. A consensus model for the regulation of glucagon secretion remains to be formulated but there is extensive information on α -cell gene expression, ultrastructure and electrical activity^{9,10}. By comparison, the δ -cell has not received much attention from islet physiologists of late and our understanding of the cell physiology of somatostatin secretion remains fragmentary. Recent findings implicate increased somatostatin signalling as a cause of the reduced counter-regulatory glucagon secretion during insulin-induced hypoglycaemia in diabetic animals^{11–13}. Conversely, insulin and glucagon secretion during high glucose are both tonically inhibited by somatostatin¹⁴ and there is evidence that hyperglucagonemia in poorly controlled diabetes can be suppressed by somatostatin^{15–17}. Indeed, an early study demonstrated that somatostatin infusion in type 1 and type 2 diabetic patients led to improved glycaemic control despite lower insulin requirements by reducing glucagon secretion and it was proposed that a long-acting somatostatin agonist may be useful as an adjunct to insulin therapy¹⁸. Collectively, these observations merit renewed interest in the δ -cell. A review on δ -cell physiology and somatostatin secretion in health and disease is therefore timely. Here we will present a model for the cellular regulation of somatostatin secretion in δ -cells and discuss the crucial role that the δ -cells play by controlling the α - and β -cells via inhibitory paracrine crosstalk. We will then turn to the impact of diabetes on somatostatin secretion and its role in the pathophysiology of diabetes. Finally, we will consider the δ -cell and somatostatin signalling as pharmacological targets.

Discovery of somatostatin and the pancreatic δ -cell

Somatostatin was originally isolated from the hypothalamus and found to inhibit the release of growth hormone (GH) in the pituitary¹⁹. Initially named as 'GH release-inhibiting hormone' it was renamed somatostatin to reflect this growth-inhibiting effect. Shortly after

its discovery, somatostatin was found to be produced and secreted in the islets of Langerhans²⁰.

Insulin and glucagon are released by the β - (B-) and α - (A-) cells of the endocrine pancreas of the pancreatic islets. The A- and B-cells were identified based on the staining properties following alcohol- and aqueous-based fixation methods. In addition, a third type of islet cell type was left unstained and referred to a 'clear' or C-cell. Subsequently another granulated cell type was identified and referred to as D-cell (or δ -cells). They are identical to the argyrophilic islet cells originally referred to as A₁/ α ₁-cells (to distinguish them from the argyrophobic glucagon-containing A₂/ α ₂-cells). It now seems clear that the C-cells were in fact D-cells (reviewed by REF²¹). With hindsight, it seems likely that somatostatin is the factor in lysates from the α ₁ cells (= δ -cells) responsible for the inhibition of insulin release^{22,23}. In this review we will refer to the different islet cells using the Greek letter nomenclature.

Somatostatin

There are two types of somatostatin: somatostatin-14 and somatostatin-28. Both forms of somatostatin are derived from the precursor pre-prosomatostatin (116 amino acids) which is cleaved into prosomatostatin (92 amino acids). Prosomatostatin undergoes C-terminal post-translational processing to generate somatostatin-14 and somatostatin-28. Both peptides are very short-lived and have a half-life of 1min in circulation. While somatostatin-28 is the dominant isoform elsewhere in the gastrointestinal tract, the pancreatic δ -cells secrete somatostatin-14, which is stored in secretory granules²⁴ and released by Ca²⁺-dependent exocytosis.

The pancreatic δ -cell

The δ -cells comprise only 5% of the islet cell number²⁵. In mouse islets, where β -cells occupy the islet core, most of the δ -cells are located in the islet 'cortex' with few δ -cells found in the islet centre. Whereas most α - and β -cells are rounded or rhomboid, the δ -cells show more complex morphology and have long, neurite-like processes (FIG. 1A) that make close contact with α -, β -, and δ -cells at some distance from the cell body, thereby enabling an extensive paracrine network. In human islets, where islet architecture is less defined, δ -cells occur throughout the islet. Direct δ - to α -cell contacts are increased in islets from patients with type 2 diabetes²⁴, raising the interesting possibility that the α -cells may be subject to stronger somatostatin-mediated paracrine inhibition in diabetic patients. The δ -cell neurite-like processes can be >20 μ m long (one-third of the average islet diameter²⁶) and may make contact with multiple α - and β -cells. This may explain the stimulation of both glucagon and insulin secretion seen in the presence of somatostatin receptor antagonists^{27–30}. Moreover, β -cells are connected via connexin36 gap junctions that ensure synchronized calcium responses and insulin secretion within each islet^{31–33}. Thus, β -cells not in direct contact with a δ -cell may be indirectly affected via gap-junctional signalling. Recently direct evidence for β - to δ -cell electrical coupling was reported³⁴.

Gastric and enteric somatostatin-secreting D-cells

In addition to the pancreatic δ -cells, somatostatin is also expressed throughout the gastrointestinal (GI) tract. It has been estimated that the gastrointestinal D-cells contain 65% of total body somatostatin and that the pancreatic islets only account for 5% and the rest found in the CNS³⁵. In fact, most of circulating somatostatin originates from the D-cells³⁶. Although these cells are notoriously difficult to study (scattered among the enterocytes as they are), by expressing fluorescent protein under the somatostatin promoter it is now possible to isolate them in sufficient numbers to perform more comprehensive transcriptomic and physiological characterization³⁷. However, the regulation of somatostatin secretion from the gastrointestinal D-cells is beyond the scope of this review and interested readers are instead referred to two recent reviews that cover aspects of this topic^{38,39}.

Pancreatic islet somatostatin secretion

FIG. 1B shows schematically the regulation of somatostatin secretion by nutrients, pharmacological agents, hormones and neurotransmitters. Agents have been divided into *stimulators* and *inhibitors*. TABLE 1 provides further details on the membrane receptor complement. In general, the regulation of somatostatin secretion in response to nutrients resembles that of insulin secretion. This is perhaps not surprising given that β - and δ -cells share an immediate common progenitor cell⁴⁰. In this section we consider how δ -cells sense nutrients. We correlate the regulation of glucagon secretion against recently published information on δ -cell transcriptomes^{41,42}.

Glucose

Glucose-induced somatostatin secretion is initiated in mouse islets somewhat lower than those required in human islets (3 vs 6mM) and saturates at concentrations above 10mM (FIG. 1C). In human islets, somatostatin secretion is initiated at 3mM and then increases linearly with the glucose concentration (in parallel with insulin secretion)⁴³. δ -cells express high levels of the high-affinity glucose transporters Glut1 (*Slc2a1*) and Glut3 (*Slc2a3*) instead of the beta cell-specific Glut2 (*Slc2a2*). δ -cells also express high levels of the glucokinase (*Gck*), which probably explains the inhibition of somatostatin secretion by the glucokinase inhibitor mannoheptulose^{44,45}. It seems likely that glucose (via its metabolism) stimulates somatostatin secretion via an increased cytoplasmic ATP/ADP ratio and closure of ATP-sensitive K⁺ channels (K_{ATP} channels) in a way similar to what has been described in β -cells⁴⁶ (see below). It is therefore surprising that the non-metabolisable glucose analogue 3-O-methyl-D-glucose also stimulates somatostatin secretion⁴⁷, i.e. without an increase in the intracellular ATP/ADP ratio. Thus, it appears that glucose, in at least some δ -cells, can stimulate somatostatin secretion by a mechanism not involving closure of K_{ATP} channels. There is some evidence for low expression of *SGLT1* (*Slc5a1*) in δ -cells^{41,42} and the ability of 3-O-methyl-D-glucose to stimulate somatostatin secretion may reflect sufficiently strong electrogenic (i.e. ability to affect the membrane potential) operation of this transporter to stimulate somatostatin release even without stimulation of ATP production.

Amino acids

Somatostatin secretion can be stimulated by the amino acids leucine and arginine^{48–52}. The ability of arginine to stimulate somatostatin secretion probably reflects the expression of the cationic amino acid transporters *Slc7a1* and *Slc7a2* (that encode CAT-1 and CAT-2, respectively)^{41,42}. In β -cells, these transporters mediate electrogenic uptake of amino acids like arginine and lysine⁵³ and thereby produce membrane depolarisation and initiate action potential firing when K_{ATP} channel activity is low (for example, in the presence of glucose). It is likely that arginine stimulates somatostatin secretion by the same mechanism. Leucine is transported via the neutral amino acid transporter *Slc7a5*, which is expressed in δ -cells^{41,42}. Leucine is, following deamidation and formation of α -ketoisocarproic acid⁵⁴, is metabolized by the Krebs cycle and probably stimulates somatostatin secretion via closure of the K_{ATP} channels.

Fatty acids

The plasma concentration of non-esterified free fatty acids (NEFA: mainly palmitate, oleate, stearate and lineoleate⁵⁵) oscillates between <0.1 mM after a meal and 0.5 mM in the fasted state³. The free fatty acid palmitate inhibits glucose-induced somatostatin secretion⁵⁶. Mouse δ -cells express high levels of the free fatty acid receptor GPR120 (*Ffar4*). Interestingly, GPR120-specific agonists inhibit somatostatin secretion and these effects are not seen in islets from *Ffar4* knockout mice⁵⁷. This selective inhibition of the δ -cell can be expected to result in relief from paracrine suppression of α - and β -cells, which may contribute to the acute palmitate-induced stimulation of both insulin and glucagon secretion^{56,58}.

δ -cell electrical activity

Like β - and α -cells, δ -cells are electrically excitable and experimental conditions that stimulate somatostatin secretion are generally associated with increased action potential firing in the δ -cells^{59–61} (FIG. 2A). The δ -cells are equipped with K_{ATP} channels of exactly the same type as those found in β - and α -cells. Expression of the K_{ATP} subunits Kir6.2 (*Kcnj11*) and Sur1 (*Abcc8*) in δ -cells is at least as high as in β -cells^{41,42}. The K_{ATP} channels are active (open) at low glucose and this maintains a negative (hyperpolarized) membrane potential in the δ -cell. Increasing glucose or application of sulphonylureas (such as tolbutamide and glibenclamide) reduces K_{ATP} channel activity, depolarizes the δ -cell and initiates action potential firing, thus accounting for the stimulation of somatostatin secretion^{44,49,62–64}. Conversely, the K_{ATP} channel activator diazoxide prevents depolarization and thereby inhibits somatostatin secretion^{59,65}.

In mouse δ -cells, the action potential originates from a membrane potential as negative as -60 mV, may reach $+30$ mV and have a duration of only a few milliseconds⁶⁶ (FIG. 2B). The voltage-gated membrane currents underlying these action potentials have been characterized in some detail⁶⁶ (See Legend FIG. 2B).

Local and systemic modulators of somatostatin secretion

In addition to the direct effects of glucose (and other nutrients) on the δ -cell, somatostatin secretion is modulated by paracrine factors (released from neighbouring α - and β -cells), circulating hormones, and neurotransmitters released by intra-islet nerve endings (FIG. 1B and TABLE 1).

Intra-islet factors

Pancreatic δ -cells express insulin receptors (*Insr*), but the action of insulin on somatostatin secretion is unclear. Anterograde infusion (i.e. in the direction of the normal blood flow) of an insulin antibody into perfused rat pancreata leads to dramatic (20-fold) stimulation of somatostatin secretion⁶⁷. Administration of exogenous insulin has variably been reported not to affect⁶⁸, inhibit⁵² or even stimulate somatostatin secretion⁶⁹. However, it should be remembered that the intra-islet interstitial insulin concentration is likely to be very high: the release of a single insulin granule (1.6 amol insulin) is sufficient to increase the insulin concentration to ~10nM, >100-fold higher than circulating levels of insulin²⁶.

The δ -cells also express low levels of the glucagon receptor (*Gcgr*) and respond to glucagon with increased somatostatin secretion^{50,70}.

Urocortin 3 (*Ucn3*) is co-released with insulin from β -cells and stimulates somatostatin secretion⁶⁵. Urocortin-3 acts via activation of the α -isoform of the CRH receptor 2 (*Crhr2*), which is selectively expressed by δ -cells within the islet⁶⁵. Genetic ablation of *Crhr2* or *Ucn3* leads to a 50–60% reduction of glucose-induced somatostatin secretion, an effect that was paralleled by a corresponding decrement in islet somatostatin content. Collectively, these observations indicate that islet somatostatin secretion is modulated by local release of urocortin 3 from β -cells.

The neurotransmitter GABA is also co-released with insulin from β -cells and stimulates somatostatin secretion in human islets⁷¹. Thus, GABA co-released with insulin and urocortin 3 may contribute to glucose-induced somatostatin secretion. In addition, there is evidence that GABA released from human δ -cells stimulates δ -cell electrical activity in an autocrine fashion⁷¹. Expression of GABA receptor subunits is low in mouse δ -cells (TABLE 1) but expression in human δ -cells is likely to be higher⁷¹.

In addition to the paracrine stimulation of the δ -cell by β -cell-derived factors (as exemplified by urocortin 3 and GABA) there is (as mentioned above) also evidence that the β -cells stimulate δ -cells by electrical coupling via gap junctions³⁴.

In mouse islets, acetylcholine (ACh) is released by cholinergic nerve endings^{46,72}. ACh has variously been reported to either stimulate⁴⁴ or inhibit^{57,63} somatostatin secretion. Mouse δ -cells express muscarinic M3 (*Chrm3*) and M4 (*Chrm4*) receptors. Whereas M3 receptors are coupled to G_q (leading to Ca²⁺ mobilization and somatostatin exocytosis), M4 receptors are coupled to G_i (resulting in suppression of somatostatin secretion). Thus, expression of these two muscarinic receptors, coupled to different canonical signalling cascades, may explain the discrepant reported effects of ACh action on somatostatin secretion.

Human α -cells release ACh in response and that this potentiates insulin secretion by activation of M3 receptors in β -cells⁷³. However, this is unlikely to be the only source of ACh within the islet. Although innervation of the human islet may be sparse⁷⁴, the existence of a ‘cephalic phase’ of insulin secretion (that is partially dependent on cholinergic inactivation and that cannot be accounted for by an elevation of plasma glucose⁷⁵) is well established.

Endocrine modulators

δ -cells express GLP-1 (*Glp1r*) as well as lower levels of GIP receptors (*Gipr*). Predictably, somatostatin secretion is stimulated by the incretin hormones GLP-1 (and agonists) and GIP and agents that increase cAMP (such as forskolin)^{48,68,76,77}.

Of the adrenergic receptors, only α_{2A} receptors (encoded by *Adra2a*) are expressed at significant levels. This is the same receptor that is responsible for the direct inhibition of insulin secretion in response to direct adrenergic inputs to the β -cell and likely accounts for the reported inhibitory effects of adrenaline on somatostatin secretion^{63,78}.

The hunger hormone ghrelin has long been known to inhibit insulin secretion, although various and sometimes conflicting mechanisms had been proposed to explain how a receptor that acts via G_{aq} (and thus predicted to stimulate intracellular Ca^{2+} release) *inhibits* insulin release. This conundrum was resolved with the discovery that ghrelin receptors (*Ghsr*) are selectively expressed in δ -cells where they mediate robust and selective secretion of somatostatin from mouse and human islets in response to ghrelin, which inhibits insulin release by a paracrine mechanism^{41,42}.

Ca^{2+} -regulated somatostatin secretion

Glucose-induced somatostatin secretion is associated with an elevation of $[Ca^{2+}]_i$. In isolated δ -cells, large $[Ca^{2+}]_i$ oscillations are observed at glucose levels as low as 3mM⁷⁹. Glucose-induced $[Ca^{2+}]_i$ oscillations are also observed in δ -cells in intact islets at 3mM glucose⁸⁰. These were suppressed by lowering glucose to 0.5mM or addition of the K_{ATP} channel activator diazoxide⁸¹.

Membrane depolarization (produced by supraphysiological extracellular K^+ concentration (see BOX 1) increases $[Ca^{2+}]_i$ and stimulates somatostatin secretion^{42,44,79,82}.

The nature of these $[Ca^{2+}]_i$ oscillations has not been conclusively established, but it is possible that they in part involve mobilization of intracellular Ca^{2+} . The role of intracellular Ca^{2+} stores in δ -cells and somatostatin secretion is suggested by the strong inhibitory effects of thapsigargin, dantrolene and ryanodine on glucose-induced somatostatin secretion⁴⁴. Dantrolene and ryanodine are inhibitors of the intracellular ryanodine receptor (RyR) Ca^{2+} release channels and thapsigargin inhibit the Ca^{2+} ATPase of the sarco-endoplasmic reticulum. A role for intracellular Ca^{2+} release is not in conflict with the observation that inhibitor that Ca^{2+} channel inhibitors (including the L-type Ca^{2+} channel blocker isradipine) inhibit somatostatin secretion⁶⁵; plasmalemmal Ca^{2+} entry may result in further Ca^{2+} release by Ca^{2+} -induced Ca^{2+} release (CICR) mediated by RyR Ca^{2+} release channels (FIG. 2C).

Transcription profiling reveals that in mouse islet, RyR expression is almost exclusively restricted to δ -cells and that RyR3 is the dominant RyR subtype^{41,42}. RyR expression in both α - and β -cells is very low. Thus, any effects of ryanodine on insulin and glucagon secretion may reflect a paracrine effect (see FIG. 3A).

The CICR-dependent component of somatostatin secretion is small at low glucose but increases with glucose with an EC₅₀ of ~10mM⁴⁴. Glucose-induced somatostatin release is nearly abolished by inhibitors of protein kinase A and the cAMP sensor Epac2 (own unpublished). Cyclic AMP (cAMP) may promote CICR by sensitising the RyR3s to Ca²⁺ (REF⁸³). How glucose increases intracellular cAMP and promotes CICR is not known, but may be the result of paracrine signaling within the islets. For example, release of urocortin-3 from neighbouring β -cells can be expected to activate adenylate cyclase and increase cAMP upon binding to the CRHR2 receptor.

Somatostatin as a paracrine regulator

Once somatostatin has been released from the δ -cell, it will exert local paracrine effects by activation of somatostatin receptors (SSTRs) in islet cells. Whether pancreatic islet somatostatin also exerts more systemic effects is not known but quantitative considerations suggest that such effects are unlikely to be of major functional significance. of somatostatin in plasma, >90% is somatostatin-28 and only 5–10% represents somatostatin-14 (the δ -cell variety of somatostatin)⁸⁴. Furthermore, pancreatectomy does not lower plasma somatostatin levels⁸⁵.

There are five different somatostatin receptors (SSTR1–5)⁸⁶. They are all coupled to an inhibitory G protein (G_i) and the effects of somatostatin can be prevented by pretreatment of pertussis toxin. It was formerly believed that β - and α -cells expression SSTR5 and SSTR2, respectively. More recent transcriptomic analyses using RNAseq on FACS-purified islet cell populations confirm that SSTR2 is the predominant receptor type in mouse and human α -cells⁸⁷ SSTR3 is expressed by mouse α - and β -cells^{41,42} (FIG. 3A). Somatostatin exerts a plethora of effects on both α - and β -cells, which collectively result in reduction of insulin and glucagon secretion (summarized in FIG. 3B). Interestingly, mouse δ -cells express SSTR1 as well as SSTR3^{41,42}, possibly suggestive of autocrine feedback control of its release. Indeed, somatostatin secretion is strongly stimulated in the presence of somatostatin receptor antagonists^{76,88,89}.

In addition to the inhibitory effects of somatostatin on hormone release, somatostatin also influences β -cell mass. Somatostatin agonists are potent suppressors of neuroendocrine tumour growth⁹⁰ and inhibit the proliferation of MIN6 insulinoma cells⁹¹ as well as mouse and human β -cells⁹², in agreement with the observation that G_i signalling inhibits β -cell proliferation⁹³. However, mice in which the somatostatin gene was ablated do not demonstrate increased β -cell mass⁶³. This argues that somatostatin does not normally suppress β -cell proliferation but it should be noted that δ -cells contribute to β -cell mass by direct transdifferentiation⁹⁴. The latter finding fits into an emerging picture of cellular plasticity and that transdifferentiation between α -, β - and δ -cells (formerly considered to be terminally differentiated) is a feature of the adjustments of islets during physiological and

pathophysiological conditions. Whether somatostatin contributes to this islet cell plasticity and the extent to which these observations apply to human islets remain open questions.

Diabetes – a somatostatin secretion disorder

Diabetes is considered a ‘bihormonal disorder’ (involving both insulin and glucagon secretion defects)⁹⁵. Given the inhibitory effects of somatostatin in both insulin and glucagon secretion, the question arises whether diabetes may involve all three major islet hormones.

Studies in perfused rat and dog pancreases indicate that somatostatin secretion at low glucose is higher than in non-diabetic control animals^{96,97,98}. Studies in rats further indicate that diabetes is associated with a reduced counter-regulatory stimulation of glucagon secretion in response to insulin-induced hypoglycaemia¹³. To our knowledge, there is no published information on the impact of diabetes on somatostatin secretion in isolated human islets. Measurements of circulating somatostatin-like immunoreactivity (SLI) indicate that a mixed meal increases plasma SLI by 10% in healthy and 20% in type 2 diabetic patients, respectively⁹⁹. How much of this stimulation that reflects δ -cell somatostatin-14 is unclear but it is clear that it only represents a small (5–10%) fraction of SLI¹⁰⁰. Studies in dogs indicate that a glucose-induced stimulation of somatostatin secretion can only be detected in the pancreatic vein and that changes in vena cava as well as the mesenteric, gastroepiploic and short gastric veins are small¹⁰¹.

Somatostatin and δ -cells – therapeutic implications

Of course, the most important question whether the δ -cell and somatostatin secretion can be pharmacologically targeted in a way that provides benefits to diabetic patients. The risk of hypoglycaemia constitutes a barrier to good glycaemic control and many insulin-dependent diabetic patients are treated less aggressively with insulin than would otherwise be the case¹⁰². There is in fact a U-shaped relationship between plasma glucose and mortality in diabetic patients with the lowest mortality in diabetic patients at an HbA1C of 7.5% (a surrogate marker of long-term glycaemic control)¹⁰³, well above that of non-diabetic individuals (5%).

As discussed above, experiments in rat models of diabetes are suggestive of impaired counter-regulatory glucagon secretion during insulin-induced hypoglycaemia due to increased somatostatin signalling^{11–13}. The consequences of somatostatin oversecretion under hypoglycaemic conditions may be corrected by preventing its biological effects. Indeed, SSTR2 antagonists restore counter-regulatory glucagon secretion during insulin-induced hypoglycaemia in diabetic rats^{11–13} but these receptors are widely expressed (stomach, adrenal medulla, cerebral cortex, hypothalamus)¹⁰⁴ and translation to human studies therefore requires safety testing. A radiolabelled SSTR2 antagonist (JR11) is used in clinical trials¹⁰⁵, which will provide information on the safety and tolerability.

Patients who have experienced one hypoglycaemic episode (due to impaired counter-regulatory glucagon secretion) have an increased risk of another¹⁰⁶. The underlying reasons for both phenomena remain unestablished. In this context, it is worth remembering that

insulin not only produces hypoglycaemia but also lowers the plasma concentration of K^+ (hypokalaemia)¹⁰⁷. Hypokalaemia is associated with increased mortality¹⁰⁸, possibly via cardiac effects¹⁰⁹. In general, hypokalaemia decreases electrical excitability. This because lowered is $[K^+]_o$ generally leads to membrane hyperpolarization (BOX 1), resultant reduction of cellular activity (secretion, nerve activity, with muscle contraction *etc.*). Paradoxically, hypokalaemia (low $[K^+]_o$) stimulates rather than inhibits somatostatin secretion¹¹⁰. The stimulation of somatostatin secretion was attributed to inhibition of the Na-K pump. The expression of the Na-K ATPase subunit *Atp1a2* is reduced by hypokalaemia¹¹¹. If hypokalaemia influences Na-K pump expression in δ -cells (δ -cells express *Atp1a1*) similarly, it can be expected to increase somatostatin release (summarized in FIG. 3C) that in turn leads to an attenuation of counterregulatory glucagon secretion and persists even after normokalaemia has been restored.

Coda

Here we have attempted to illustrate the important roles played by the δ -cells and somatostatin in ‘health and disease’. It is clear that the islets are very complex structures and that they, via the paracrine cross-talk’ are much more than the ‘sum of the parts’. The δ -cells is emerging as a master regulator within the islet and represents an interesting and novel pharmacological target through which dysregulated insulin and glucagon secretion in diabetes may be corrected. Indeed, by virtue of their capacity of restoring counter-regulatory glucagon secretion SSTR2 antagonists should be considered as an adjunct to insulin therapy, thereby enabling more aggressive insulin treatment by minimising the risk of hypoglycaemia.

Acknowledgments

We thank Dr Q Zhang for providing the confocal image of δ -cells in an intact islet. Work discussed in this review was supported by a Wellcome Trust Senior Investigator Award, the Knut and Alice Wallenberg Foundation, the Swedish Research Council, the Hartwell Foundation for Biomedical Research (201500731), the Juvenile Diabetes Research Foundation (CDA-2-2013-54) and the National Institutes of Health (DK110276).

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BOX 1

The potassium (K^+) equilibrium potential (E_K) is given by the Nernst equation

$$E_K = -61\text{mV} * \log_{10}\left(\frac{[K^+]_i}{[K^+]_o}\right)$$

where $[K^+]_i$ and $[K^+]_o$ represent the intra- and extracellular K^+ concentrations, respectively.

Assuming that the intra- ($[K^+]_i$) and extracellular K^+ concentrations ($[K^+]_o$) are normally 110 and 5mM, E_K can be estimated to be -81mV (close to the normal resting potential).

Increasing $[K^+]_o$ to 50mM (as commonly used experimentally) will change E_K to -21mV (thus opening Ca^{2+} channels and stimulating somatostatin secretion).

Conversely, a drop in $[K^+]_o$ to 2.5mM shifts E_K to -100mV (thus inhibiting electrical activity and somatostatin secretion).

Key points

- The δ -cells of the pancreatic islets secrete somatostatin, a powerful paracrine inhibitor of both insulin and glucagon secretion from islet β - and α -cells
- δ -cells are electrically excitable and glucose stimulates action potential firing and somatostatin secretion by both metabolic and non-metabolic effects in δ -cells
- Factors released by the β -cells stimulate somatostatin secretion, thereby providing a mechanism for feedback control of insulin and glucagon secretion during hyperglycemia.
- Diabetes is associated with impaired glucagon secretion in response to hypoglycaemia; an effect corrected by somatostatin antagonists, suggesting that diabetes may involve hypersecretion of somatostatin during hypoglycaemia.
- Agents that inhibit somatostatin secretion/action may reduce the risk of insulin-induced hypoglycaemia and should be considered as an adjunct to insulin therapy

Figure 1.

Somatostatin secretion and δ -cell histology. **a** | δ -cells in mouse islets. Note that some δ -cells possess processes (arrows) that extend for tens of microns. Image supplied by Dr Q Zhang (Oxford) (Methods as in REF⁴⁴). **b** | Regulation of somatostatin secretion by nutrients, hormones/neurotransmitters and pharmacological agents. Compounds that (have been reported to) stimulate somatostatin secretion shown left in black and those that inhibit release to the right in red. **c** | Parallel measurements of somatostatin (red) and glucagon (black) secretion. Data taken from (REF⁴³). 100% and 0% correspond to the maximum and the minimum secretion, respectively. The grey rectangle highlights that glucagon secretion is regulated at glucose concentrations that have little effect on somatostatin secretion.

Figure 2.

Regulation of somatostatin secretion by δ -cell electrical activity. **a** | Electrical activity at 1 and 20mM glucose recorded from a δ -cell in an intact mouse δ -cell. Cell type identified as described in (REF⁶⁶). The Na^+ channel blocker tetrodotoxin (TTX) was added as indicated. Data taken from (REF⁶¹). Note suppression of action potential firing in the presence of TTX. **b** | Two successive action potential recorded from mouse δ -cell (left) and contribution of different voltage-gated ion channels to depolarization, repolarization and interval between two successive action potentials as deduced from electrophysiological⁶⁶ and transcriptomic analyses^{41,42}. The action potential is initiated by opening of ‘low-threshold’ T-type Ca^{2+} channels (Ca_T ; specifically $Ca_V3.2$). The upstroke of the action potential involves opening of voltage-gated Na^+ channels (Na_V ; $Na_V1.3$ and/or $Na_V1.7$) and high-threshold voltage-gated L- (Ca_L ; specifically $Ca_V1.3$) and P/Q-type ($Ca_{P/Q}$; $Ca_V2.1$) Ca^{2+} channels. The downstroke (repolarising phase) of the action potential involves opening of A-type K^+ currents (specifically $K_V4.1/4.2$) with some contribution of delayed rectifying K^+ channels (K_V ; specifically $K_V1.5$ and $K_V2.1$). In the interval during two successive action potential, the K_V channels that activated during the action potential deactivates slowly and this, together with the recovery from inactivation of Na_V and Ca_T explains the ‘pacemaker’ depolarization. Single-cell transcriptomics¹¹² indicates a similar ion channel complement in human δ -cells. **c** | Stimulus-secretion coupling in a (mouse) δ -cell. Glucose uptake (via Glut1 and Glut3) leads to stimulation of glucose metabolism (glycolysis and mitochondria) and an increased cytoplasmic ATP/ADP ratio. This closes K_{ATP} channels in the plasma membrane,

producing membrane depolarization ($\Psi \downarrow$) and action potential firing, culminating in Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCC). The K_{ATP} channel activity is lower than in β -cells, which might explain why somatostatin secretion is initiated at lower glucose concentrations than insulin secretion. Ca^{2+} influx associated with electrical activity triggers further increase in cytoplasmic Ca^{2+} ($[\text{Ca}^{2+}]_i$) by Ca^{2+} -induced Ca^{2+} release (CICR) in the sarco/endoplasmic reticulum (sER) by activation of ryanodine receptor 3 (Ryr3) Ca^{2+} release channels. The resultant increase in $[\text{Ca}^{2+}]_i$ triggers somatostatin secretion. Glucose stimulation is also associated with elevation of cAMP, which may be produced be secondary to the glucose-induced $[\text{Ca}^{2+}]_i$ increase and/or stimulation by glucagon (released by neighbouring α -cells following activation of the glucagon receptor: GCGR), urocortin-3 (released by β -cells and following activation of CRHR2a) or circulating GLP-1. Cyclic AMP sensitises the Ryr3 channels to the increase in $[\text{Ca}^{2+}]_i$ and thereby facilitates CICR. Inhibitors of the Ca^{2+} ATPase (' Ca^{2+} pump') of the sER (SERCA inhibitors; e.g. thapsigargin) inhibit somatostatin secretion by depleting sER of Ca^{2+} . Ca^{2+} channel blockers inhibit somatostatin secretion by reducing the Ca^{2+} influx that triggers CICR. Stimulation and inhibition indicated by dashed arrows and + and -, respectively. Upward and downward arrows indicate an increase in concentration or membrane hyperpolarisation.

Figure 3.

Somatostatin signalling in pancreatic islets. **a** | Schematic of somatostatin signalling in the islet. Somatostatin released from δ -cells activates SSTR2 (but also some SSTR3) in adjacent α - (1) and SSTR3 in β -cells (2) that are in close proximity to the δ -cell. In addition, somatostatin released from the δ -cells may exert an autocrine inhibitory effect by activation of SSTR1 or SSTR3 in the δ -cell itself (3). **b** | Effects of somatostatin in α - and β -cells. Activation of SSTR2 leads to: *i*) inhibition of adenylate cyclase, thereby resulting in lower cytoplasmic cAMP ($[cAMP]_i$)¹¹³ and less cAMP-induced exocytosis; *ii*) inhibition of

voltage-gated Ca^{2+} channels: *iii*) activation of G protein-regulated GIRK channels (producing membrane repolarization and inhibition of electrical activity)^{114,115}; and *iv*) a direct inhibitory effect on exocytosis independent of $[\text{cAMP}]_i$ and that may involve activation of the protein phosphatase calcineurin¹¹⁵. **c**) Schematic how hypokalaemia (associated with insulin therapy) may stimulate somatostatin secretion. The Na-K pump is electrogenic and for every ATP hydrolysed 3 Na^+ and 2 K^+ are transported across the cell membrane in opposing directions, leading to a net loss of a positive charge inside the cell. Thus, the activity of the pump tends to repolarise the membrane potential ($\Psi \uparrow$) (1). In addition, the activity of the pump may lower the submembrane ATP/ADP ratio, which maintains the K_{ATP} channels in the open state (potentially leading to further repolarization) (2). Inhibition of the pump (by lowering $[\text{K}^+]_o$) leads to membrane depolarisation by removal of the repolarising influence of the Na-K pump and exerting an ATP-sparing effect (the Na-K pump accounts for up to 50% of energy expenditure¹¹⁶) leading to closure of K_{ATP} channels. This leads to the initiation of electrical activity and Ca^{2+} entry/CICR (3) and stimulation of somatostatin release (4). Reduced expression of the Na-K pump (following hypokalaemia) may exert similar effects, thus increasing somatostatin secretion under hypoglycaemic conditions. This may account for the increased risk of recurrent hypoglycaemia (via reduced counter-regulatory glucagon secretion) in some insulin-treated patients.

TABLE 1

Overview of receptors that are expressed by pancreatic delta cells and their effect on somatostatin secretion.

Ligand	Receptor name	Gene symbol	Expression level (RPKM) ^{a, b}	Effect on secretion
Ucn3	CRHR2α	<i>Crhr2</i>	5.14	stimulates
ghrelin	GHSR	<i>Ghsr</i>	48.44	stimulates
GLP1	GLP1R	<i>Glp1r</i>	39.91	stimulates
GIP	GIPR	<i>Gipr</i>	13.70	stimulates
GABA	Ionotropic (GABAA) and metabotropic (GABAB)	<i>Gabra1–5, Gabrb1–3, Gabrd, Gabre, Gabrg1–3, Garbrp, Gabrq, Gabrr1,2 subunits</i>	Multiple genes, expression invariably low.	stimulates
Acetylcholine	Muscarinic M3	<i>Chrm3</i>	2.71	stimulates
	Muscarinic M4	<i>Chrm4</i>	22.05	inhibits
Adrenaline	α2a adrenergic receptor	<i>Adra2a</i>	9.72	inhibits
Somatostatin	SSTR1	<i>Sstr1</i>	18.28	inhibits
Palmitate/NEFA	GPR120	<i>Ffar4</i>	60.89	inhibits
insulin	INSR	<i>Insr</i>	12.16	conflicting reports
Glucagon	GCGR	<i>Gcgr</i>	5.62	stimulates

^a reads per kilobase of gene model per million reads sequenced (data from REF⁴²).

^b RPKM values provide a useful approximation of actual receptor expression levels, but many post-transcriptional processes contribute to the actual cell-surface expression of receptor protein.