Title

The Difference δ-Cells Make in Glucose Control

Journal

Physiology, 33(6)

ISSN

1548-9213

Authors

Huising, Mark O

van der Meulen, Talitha

Huang, Jessica L

et al.

Publication Date

2018-11-01

DOI

10.1152/physiol.00029.2018

The Difference Delta Cells Make in Glucose Control

Mark O. Huising[1,2*], Talitha van der Meulen[1], Jessica L. Huang[1], Mohammad S. Pourhosseinzadeh[1], Glyn M. Noguchi[1]

[1]Department of Neurobiology, Physiology & Behavior, College of Biological Sciences, University of California, Davis, CA 95616, USA

[2]Department of Physiology and Membrane Biology, School of Medicine, University of California, Davis, CA 95616, USA

* Contact: mhuising@ucdavis.edu

Abstract

The role of beta and alpha cells to glucose control are established, but the physiological role of delta cells is poorly understood. Delta cells are ideally positioned within pancreatic islets to modulate insulin and glucagon secretion at their source. We review the evidence for a negative feedback loop between delta and beta cells that determines the blood glucose set point and suggest that local delta cell-mediated feedback stabilizes glycemic control.

Introduction

Over half of US adults are now estimated to have diabetes or pre-diabetes (44). Type 1 diabetes (T1D) is caused by the autoimmune destruction of beta cells, while Type 2 diabetes (T2D) results from peripheral insulin resistance precipitated by factors associated with lifestyle and genetic predisposition. Both diseases are characterized by absolute (T1D) or relative (T2D) insulin deficiency. Consequently, pancreatic beta cells have been studied intently for decades. Less appreciated is that excess glucagon secretion from pancreatic alpha cells is responsible for as much as half of the hyperglycemia in diabees (77), which is the immediate cause for most diabetes-related complications. Successful diabetes management therefore requires effective strategies to not only restore insulin or improve insulin action, but to prevent glucagon-induced hepatic glucose production from aggravating hyperglycemia. Here we make the case that pancreatic delta cells provide crucial feedback control of alpha and beta cells to coordinate insulin and glucagon secretion in healthy islets that breaks down in diabetes.

The pancreatic islet is home to more than beta cells.

The principal endocrine output of the pancreatic islets are insulin and glucagon. During and shortly after feeding nutrients absorbed across the intestinal epithelia stimulate insulin secretion. Conversely, under catabolic conditions that occur between meals or during a fast, beta cells are silent as alpha cell activity increases to safeguard against hypoglycemia. Healthy islets are capable of balancing insulin and glucagon output with tremendous precision. This is illustrated by continuous glucose monitoring (CGM) experiments in mice (78) that reveal the narrow range within blood glucose is maintained over multiple diurnal cycles despite *ad libitum* food access. Similarly, a healthy human pancreas maintains euglycemia over 87,000 meals consumed in a

lifetime[1]. While alpha and beta cells each possess the ability to sense glucose in a cell-autonomous fashion, it is no coincidence that they are organized in close proximity within the islets of Langerhans. This arrangement enables careful coordination between insulin and glucagon at their source by a potent combination of paracrine, neural, and endocrine inputs (Figure 1A). Among the most prominent of these signals is somatostatin released by pancreatic delta cells (62), which make up approximately 5-10% of the endocrine cells within the islet.

Discovery of delta cells

Pancreatic delta cells were first recognized as a distinct cell type from alpha and beta cells based on alcohol- and aqueous-based histological staining methods, and were originally referred to as A1 cells, C cells, gamma cells, or D cells (3). These cells had no known function and were considered to represent a distinct functional stage of alpha or beta cells. This changed with the discovery that somatostatin, a novel hypothalamic peptide named for its ability to suppress somatic growth by inhibiting growth hormone (11), is found in all pancreatic delta cells (21, 32). Synthetic somatostatin peptide was subsequently confirmed to potently inhibit insulin and glucagon secretion from isolated islets (13). However, the pancreatic delta cell has long been understudied, in part because it has been challenging to quantify the impact of local delta cell-dependent feedback on alpha and beta cells. The physiological importance of delta cell-mediated feedback on insulin and glucagon release is only now coming into focus.

Paracrine crosstalk within pancreatic islets

[1] *Assuming three meals a day, average US life expectancy of 79.56 years (source: cia.gov/library/publications/the-world-factbook/fields/2102.html).*

While beta and alpha cell activity is inextricably tied to glucose levels, many signals from inside and outside the islet ultimately contribute to shape the final insulin and glucagon output. Insulin release from beta cells is triggered when glucose exceeds a threshold of approximately 7 mM glucose (16, 80) (Figure 1B). Glucose-stimulated insulin secretion (GSIS) can be further amplified via the actions of incretin hormones such as glucagon-like peptide-1 (GLP-1). GLP-1 activates its cognate GLP-1 receptor (GLP1R), a Gαs-coupled class B GPCR abundantly expressed on beta cells. This amplifying pathway is largely ineffective below the glucose threshold of beta cells, preventing incretins from stimulating insulin release under low glucose. This greatly reduces the risk of insulin-induced hypoglycemia, which underlies the success and safety of incretin-based therapies in treating T2D.

Control of glucagon release is complex and follows a biphasic response to glucose (Figure 1B). Maximal glucagon secretion occurs under low glucose and decreases towards a nadir around 5 mM glucose (24, 43, 80). Alpha cells are directly suppressed by glucose via an alpha cell-intrinsic mechanism that involves K_{ATP} channel inhibition (80). On top of the direct stimulatory effects of low glucose, alpha cells respond robustly to adrenergic stimulation as part of the counterregulatory response to hypoglycemia (75). A rise in glucose beyond 5 mM activates an ER Ca^{2+} store-operated mechanism that – paradoxically – facilitates glucagon release under hyperglycemic conditions (41, 80). It has long been known that glucagon *stimulates* insulin secretion (66, 67), even though the systemic actions of glucagon functionally oppose those of insulin. This effect is mediated by the glucagon receptor (GCGR), a class B GPCR related to the incretin receptors that like GLP1R is Gαs-coupled and expressed by beta cells (Figure 1). Glucagon essentially acts in an incretin-like fashion to amplify GSIS within the islet. In fact, the most recent evidence suggests that glucagon from alpha cells may be required for full GSIS in

response to hyperglycemia (59). Glucagon secretion is suppressed by beta cell-dependent inhibitory control (28, 29), which is often attributed to the direct inhibitory actions of beta cell-derived factors such as insulin, GABA and Zn^{2+} on alpha cells (22, 43, 53, 60, 80, 83). However, none of these beta cell-derived factors has consistently emerged as the predominant inhibitor of alpha cell activity. Therefore, the possibility of beta cell-dependent activation of delta cells that inhibits alpha cells via somatostatin during hyperglycemia is likely. Collectively, this illustrates how hormone release from the islets is controlled by a complex – at times paradoxical - web of paracrine interactions.

The delta cell provides paracrine feedback within the islet

Delta cells are organized together with alpha cells around the mouse islet periphery, where they envelop a core of beta cells. In humans, they are intermingled with the other endocrine cell types. Delta cells release a 14 amino acid form of somatostatin (Sst-14) that is proteolytically cleaved from a larger precursor (50). Somatostatin is also released from other peripheral sites, notably from enteroendocrine D cells in the gastrointestinal (GI) tract, which primarily secrete a larger, 28 amino acid form (Sst-28). Circulating somatostatin concentrations are largely unaffected by pancreatectomy and therefore do not reflect pancreatic delta cell activity (25, 74). Instead, the GI tract is the major source of circulating somatostatin, which may influence islet beta and alpha cells (14, 42). Nevertheless, circulating somatostatin (~5-25 pM) is an order of magnitude below the IC50 and EC50 values of somatostatin receptors (55, 56), suggesting that delta cells are the predominant source of somatostatin within the islet. Therefore, the main function of the pancreatic delta cell is to provide feedback control of neighboring beta and alpha cells via local circulation and the interstitial compartment (13, 65). The inhibitory actions of somatostatin are mediated via

five somatostatin receptors, SSTR1 – SSTR5. These are class A GPCRs that generally inhibit their target cells by activating the inhibitory Gαi protein or G protein-coupled inwardly rectifying K^+ (GIRK) channels (50). Islets or beta cells have been suggested to express each of the somatostatin receptors, mostly by antibody-dependent methods that critically depend on the quality and careful validation of the reagents (reviewed by 9, 38, 50, 51). However, comprehensive alpha, beta and delta cell transcriptomes do not support much of this prior work. While it is true that somatostatin receptors are expressed by each of the islet cell types (Figure 1A), abundant expression of Sstr2 by alpha cells is the only aspect that unequivocally holds up from these earlier reports (reviewed by 1, 20). Mouse beta cells abundantly (but not exclusively) express Sstr3, which is rarely mentioned in reviews of islet somatostatin receptors. Somatostatin secretion is stimulated dose-dependently by glucose in a linear fashion (Figure 1B) (65, 82). But even below the glucose threshold for beta cells, alpha cells are activated upon the addition of somatostatin antagonists, suggesting that significant basal somatostatin tone restrains alpha cell activity across the glucose spectrum. In addition to glucose, sulfonylureas, amino acids and cAMP are all capable of stimulating somatostatin secretion (2, 10, 23, 34, 69). However, until recently, the physiological cues that govern delta cell activity during normal glucose metabolism were not understood.

Urocortin3 is required for normal glucose-stimulated somatostatin secretion

We discovered that normal glucose-stimulated somatostatin secretion (GSSS) requires the peptide hormone Urocortin 3 (UCN3), which is related to corticotropin-releasing hormone (CRH) and activates the type 2 CRH receptor (CRHR2). UCN3 is the 3rd most abundant beta cell hormone after insulin and amylin and is co-released with insulin from beta cells (40, 78). UCN3 selectively activates delta cells, which express the α isoform of CRHR2 (20, 33), to release somatostatin. This

finding closed a novel intra-islet negative feedback loop that is initiated by beta cell release of UCN3 to promote delta cell somatostatin secretion, which inhibits beta cells. Indeed, *Ucn3* null mice show impaired somatostatin secretion, which can be fully rescued by addition of synthetic UCN3 peptide (78). Predictably, the impaired somatostatin secretion enables exaggerated first- and second phase GSIS, which is also immediately normalized upon perfusion with synthetic UCN3. This *Ucn3* null phenotype closely resembles the phenotype of somatostatin null mice, which also demonstrate an exaggerated first- and second-phase GSIS that is acutely normalized by the supplementation of synthetic somatostatin peptide (26). The similar phenotype of the null mice offers strong support for the participation of UCN3 and somatostatin in the same feedback loop. Blocking endogenous UCN3 with the selective CRHR2 peptide antagonist Astressin2b (Ast2b) (56) prevents GSSS from mouse and human islets (78). This demonstrates that during hyperglycemia, endogenous Ucn3 released from beta cells is necessary and sufficient for somatostatin secretion, which proceeds to inhibit beta cells. Taken together, these observations have established that UCN3 activates a beta cell-dependent, delta cell-mediated negative feedback loop to attenuate insulin secretion.

Bidirectional exchange of paracrine signals within the islet

The paracrine role of delta cell and the viability of the UCN3-mediated negative feedback loop rests on the ability of delta cells to efficiently receive and relay signals within the islet. Crosstalk is often considered to occur via intra-islet capillary circulation, but there is no consensus whether circulation in the rodent islets favors mantle-to-core communication (46, 49) or vice versa (8, 48, 68). Several factors favor the model of a feedback loop mediated by UCN3 and somatostatin that relies on a bidirectional exchange of signals between in the mantle and beta cells in the core.

First, there is emerging evidence that islet blood flow is dynamically regulated (19). Second, somatostatin and/or UCN3 may reach their target cells by diffusion through the interstitial space. Third, beta cells within an islet are electrically coupled via Connexin-36 gap junctions (5, 27), implying that not every individual beta cell needs to be directly suppressed by somatostatin to ensure effective inhibition of all beta cells within an islet. Fourth, mouse delta cells have axon-like projections that enable the release and receipt of signals at some distance from the cell body and make them readily distinguishable from beta and alpha cells (Figure 2A). Finally, adult human islets feature a more random intermingling of alpha, beta, and delta cells (Figure 2B) that would only be more conducive to the bidirectional feedback between beta and delta cells first identified in mouse islet. Interestingly, human delta cells lack the characteristic axon-like projections of mouse delta cells and are significantly more compact than mouse delta cells (Figure 2C), which may represent a morphological correlate of the distribution of delta cells throughout the human islet.

The beta cell as a blueprint for the delta cell

The discovery that UCN3 is required for normal GSSS raised the question whether delta cells respond directly to glucose at all, or if GSSS can be fully accounted for by the paracrine actions of UCN3. To develop a working model of the relative contributions of glucose and paracrine signals such as UCN3 on delta cell activity, it is helpful to turn to the beta cells. Beta cells share an immediate precursor with delta cells in pancreas development (70) and the mechanistic basis of their activation has been extensively studied. Beta cell activation is triggered by the uptake of glucose by passive diffusion through glucose transporters, followed by its stepwise catabolism via the TCA cycle and oxidative phosphorylation yielding ATP. The increased

ATP/ADP ratio closes ATP-sensitive K^+ leak (K_{ATP}) channels, which causes accumulation of K^+ and depolarization of the beta cell. This triggers opening of voltage-gated Na^+ and L-type Ca^{2+} channels. The resulting Ca^{2+} influx stimulates exocytosis of secretory granules (reviewed by 61).

A number of studies have suggested that beta and delta cells share common mechanisms of activation. Diazoxide, which keeps the K_{ATP} channel complex in the open conformation to prevent depolarization and the L-type calcium channel blocker isradipine, block both insulin and somatostatin secretion when applied to intact islets (10, 78). Importantly, exogenous UCN3 fails to rescue both diazoxide- and isradipine-mediated inhibition of somatostatin secretion (78). This demonstrates that the closure of delta cell K_{ATP} channels and the influx of Ca^{2+} via L-type channels in response to glucose is necessary for normal somatostatin secretion. However, somatostatin release from islets null for *Ucn3* is only modestly (but significantly) stimulated by glucose and can be fully rescued by synthetic UCN3 (78). This proofs that the bulk of 'glucose-stimulated' somatostatin release actually depends on local UCN3. Overall, this favors a model where delta and beta cells use similar mechanisms to trigger hormone release in response to glucose, and further amplify it by Gαs-mediated signaling. Where delta cells differ from beta cells is in the identity of the signals that amplify glucose-stimulated hormone secretion, with locally released UCN3 the principal paracrine signal to stimulate delta cells, while beta cells respond instead to incretins and glucagon (Figure 1A).

The delta cell as a modulating hub that shapes islet cell activity

While UCN3 is the principal paracrine signal to stimulate somatostatin secretion, delta cells respond to a multitude of paracrine, endocrine and neural signals. For example, the potent insulinostatic actions of the hunger hormone ghrelin (17, 18, 54, 76, 84) are mediated indirectly

via the stimulation of somatostatin release from delta cells (1, 20). And long-chain free fatty acids, such as palmitate, stimulate insulin secretion not just directly via the stimulation of GPR40 and enhanced beta cell intracellular metabolic rate (35, 37), but also indirectly by suppressing somatostatin secretion via the inhibitory receptor GPR120 expressed by delta cells (72). Adrenosympathetic inputs (*i.e.* catecholamines) stimulate alpha cells via β1 adrenergic receptors as part of the counterregulatory response to hypoglycemia. Simultaneously, beta and delta cells are inhibited via α2 adrenergic receptors, which suppress insulin secretion and facilitate de-repression of alpha cells from somatostatin-mediated inhibition, respectively (20, 57). Delta cells are also suppressed by cholinergic inputs from autonomic innervation in mouse islets, or from acetylcholine release by human alpha cells (58). Recent transcriptomes from mouse (1, 4) and human (39) delta cells have validated the delta cell-selective expression of these receptors, and suggest furthermore that receptors for leptin (LEPR) and dopamine (DRD2) are expressed by human, but not mouse delta cells. Collectively, these observations cast the delta cell as a central hub within the islet that translates inputs from paracrine and endocrine signals, nutrients, and neurotransmitters into appropriate intra-islet feedback inhibition via somatostatin (Figure 1) (39).

Local feedback inhibition by delta cells determines the set point for plasma glucose

The physiological significance of delta cell paracrine signaling is highlighted by the role of the Ucn3-induced, delta cell-mediated negative feedback loop in postnatal development. Full expression of endogenous UCN3 does not occur until 2-weeks post-partum (P14) and coincides with a notable attenuation of plasma insulin and rise in glucose levels at this young age in mice (6, 79). To establish causality, we generated a doxycycline-inducible beta cell-specific bitransgenic mouse model to induce endogenous levels of UCN3 specifically within insulin-expressing cells

with an onset and duration of our choosing (78). We induced UCN3 prematurely by administering doxycycline to pregnant dams incapable of UCN3 induction from E10.5 onwards. This resulted in a premature increase in plasma glucose in bitransgenic offspring, which reflect the premature onset of UCN3-driven, somatostatin-mediated inhibition of insulin (Figure 3A, B). In control littermates this feedback does not set in until full expression of endogenous UCN3 after P14. This experiment established that the onset of local inhibitory feedback by pancreatic delta cells on insulin release determines the homeostatic set point for plasma glucose. Since the induction of UCN3 is restricted to pancreatic beta cells and remains undetectable in blood, we successfully isolated the effect of pancreatic delta cells from the potentially confounding contributions of somatostatin by other sources, such as the enteroendocrine D cells responsible for most of the circulating somatostatin (25, 74).

The benefit of feedback inhibition by delta cells

As a field, the focus on restoring beta cell mass and function to increase insulin output and better manage diabetes makes it easy to forget that negative feedback regulation is a fundamental principle in biology to which beta cells are no exception. What then is the benefit of a delta cell-mediated feedback mechanism that inhibits insulin secretion? Unlike incretin hormones which can only amplify insulin secretion during hyperglycemia and are therefore relatively safe from stimulating insulin during hypoglycemia, insulin itself has very real potential to cause dangerous episodes of hypoglycemia. Indeed, insulin-induced hypoglycemia is a major risk factor that contributes to the death of too many patients who manage their diabetes with insulin (15). Somatostatin-mediated feedback control on beta cells is the mechanism by which healthy islets prevent excess insulin release. This feedback control must be robust because even a single

hypoglycemic episode can be fatal. Our working model is that the benefit of delta cell-mediated feedback 1) prevents hyperinsulinemia-induced hypoglycemia and 2) ensures stable euglycemia with minimal deviations from the glucose set point.

Insulin secretion under hyperglycemia is pulsatile and driven by beta cell autonomous mechanisms (31, 45). Somatostatin secretion is also pulsatile, synchronized with beta cells, but trails insulin release by 30 seconds to a few minutes (28, 29, 65). While somatostatin secretion is triggered by glucose alone below the glucose threshold of beta cells (Figure 1B), the majority of somatostatin release during hyperglycemia depends on UCN3 from beta cells (78), which may account for the delay in somatostatin secretion. A model where somatostatin secretion directly depends on the paracrine actions of beta cell-derived UCN3 ensures: 1) synchronicity of delta and beta cell activity, 2) proportionality between the degree by which plasma glucose and insulin have deviated from their set point and the strength of the ensuing negative feedback, 3) that delta cell-mediated feedback control of insulin secretion is activated with an intrinsic delay. The purpose of negative feedback is not to prevent the initiation of insulin secretion in the face of hyperglycemia; that would lead to diabetes. A delay in somatostatin secretion ensures that the initial insulin secretion in response to hyperglycemia proceeds uninhibited. But thereafter, what we consider to be GSIS is in fact the net result of the simultaneous stimulation of beta cells with glucose and inhibition with somatostatin (Figure 4A). We propose that such feedback inhibition on beta cells is instrumental in precisely attenuating insulin secretion *in anticipation of* the return of plasma glucose to its homeostatic set point (Figure 4A). This prevents overshooting of insulin, which would cause a hypoglycemic excursion.

Recently, two reports suggested that delta cells are directly coupled to beta cells via gap junctions to explain the synchronicity of pulsatile insulin and somatostatin responses (12, 81), a

possibility that had previously been ruled out (47). Indeed, this would lead to instant activation of delta cells upon beta cell activation and could not account for the delay in pulsatile somatostatin release compared to insulin. We have looked at the responses of several thousand delta cells within intact islets and have yet to observe clear evidence of direct gap-junction connections between delta and beta cells (Huising lab, unpublished).

Loss of UCN3 from beta cells early in diabetes increases glycemic volatility

UCN3 is one of the first beta cell markers to disappear in pre-diabetes (78). The mechanistic basis for this rapid downregulation is not well understood, beyond the observation that treatment with pro-inflammatory cytokines *in vitro* (7) or exposure to a pro-inflammatory environment in the context of the Non-Obese Diabetic (NOD) mouse model of T1D (63) cause a loss of beta cell Ucn3 expression. Treatment with the beta cell toxin streptozotocin similarly causes the downregulation of Ucn3, suggesting that the STZ-induced Nitric Oxide (NO) and Reactive Oxygen Species (ROS) cause oxidative stress (73) that inhibits Ucn3 expression (78). Regardless of the mechanism(s) responsible for the downregulation of Ucn3 in diabetes, the loss of UCN3 deprives delta cells of the principal signal they need to secrete somatostatin in response to hyperglycemia (78), even though delta cells numbers are relatively unaffected in diabetes (30, 52, 64, 71). Indeed, restoration of endogenous levels of Ucn3 in diabetic beta cells using a doxycycline-inducible mouse model secondary to the loss of Ucn3 in T2D aggravated diabetes (78), likely by increasing somatostatin-mediated suppression of insulin. Loss of Ucn3 during diabetes is therefore partially adaptive response that maximizes insulin output in the face of increasing peripheral insulin resistance in T2D (78). However, this comes at the expense of local feedback inhibition of beta cells. Under circumstances where normal Ucn3 and somatostatin-

mediated feedback control of beta cells breaks down, GSIS truly becomes dependent on glucose alone. The absence of negative feedback initially allows for excess insulin secretion (Figure 4B), with extended insulin action causing plasma glucose to overshoot its set point, activating counterregulation and contributing to glycemic volatility. Indeed, by CGM of *ob/ob* mice we observed markedly increased glycemic volatility in addition to severe hyperglycemia (78). More recently, it was shown that the onset of T1D in NOD mice and T2D in ZDF rats is characterized by a marked increase in the amplitude of glucose excursions (36, 85). This observation is consistent with the progressive loss of UCN3 – and the feedback control it triggers – prior to the autoimmune-mediated demise of beta cells that causes full-blown hyperglycemia (63).

Summary and Conclusions

Pancreatic delta cells are emerging as important contributors that are well-positioned to modulate insulin and glucagon secretion directly at their source. The intra-islet feedback inhibition that delta cells provide to beta and alpha cells is essential for precise control and coordination of insulin and glucagon secretion. These interactions are necessary for stable glycemic control and determine the homeostatic set point for glucose. In addition to their paracrine activation by UCN3, delta cells receive selective inputs from multiple hormones, neurotransmitters, and nutrients and integrate these into appropriate feedback modulation of insulin and glucagon secretion. Finally, loss of normal delta cell-mediated feedback inhibition occurs early in diabetes and likely contributes significantly to glycemic volatility and other aspects of the pathophysiology of diabetes, including excess glucagon secretion during hyperglycemia. As we better appreciate the physiological contribution of delta cells to glucose homeostasis we would be remiss if we did not consider delta cells and somatostatin as therapeutic targets to realign insulin and glucagon release

in diabetes. Although sustained restoration of Ucn3 in T2D aggravated hyperglycemia (78), this observation does not disqualify delta cell-dependent feedback as a target in T2D. It merely indicates that continuous activation of delta cell-dependent feedback in diabetes is no more advisable than the continuous administration of insulin in diabetes. Analogous to insulin, there is a need to align delta cell release of somatostatin with the time its actions are most protective, whether by preventing episodes of hyperinsulinemic hypoglycemia or by curbing excess glucagon secretion in T2D.

Acknowledgements

This work was supported by grants from the National Institutes of Health (NIDDK110276) and the Juvenile Diabetes Research Foundation (CDA-2-2013-54) to MOH. JLH and GMN were supported by a NIGMS-funded Pharmacology Training Program (T32GM099608). The authors report no conflicts of interest.

References

1. **Adriaenssens AE, Svendsen B, Lam BY, Yeo GS, Holst JJ, Reimann F, and Gribble FM.** Transcriptomic profiling of pancreatic alpha, beta and delta cell populations identifies delta cells as a principal target for ghrelin in mouse islets. *Diabetologia* 59: 2156-2165, 2016.
2. **Barden N, Alvarado-Urbina G, Cote JP, and Dupont A.** Cyclic AMP-dependent stimulation of somatostatin secretion by isolated rat islets of Langerhans. *Biochemical and biophysical research communications* 71: 840-844, 1976.
3. **Baskin DG.** A Historical Perspective on the Identification of Cell Types in Pancreatic Islets of Langerhans by Staining and Histochemical Techniques. *J Histochem Cytochem* 63: 543-558, 2015.
4. **Benner C, van der Meulen T, Caceres E, Tigyi K, Donaldson CJ, and Huising MO.** The transcriptional landscape of mouse beta cells compared to human beta cells reveals notable species differences in long non-coding RNA and protein-coding gene expression. *BMC Genomics* 15: 620, 2014.
5. **Benninger RK, Hutchens T, Head WS, McCaughey MJ, Zhang M, Le Marchand SJ, Satin LS, and Piston DW.** Intrinsic islet heterogeneity and gap junction coupling determine spatiotemporal Ca(2)(+) wave dynamics. *Biophysical journal* 107: 2723-2733, 2014.
6. **Blum B, Hrvatin SS, Schuetz C, Bonal C, Rezania A, and Melton DA.** Functional beta-cell maturation is marked by an increased glucose threshold and by expression of urocortin 3. *Nat Biotechnol* 30: 261-264, 2012.
7. **Blum B, Roose AN, Barrandon O, Maehr R, Arvanites AC, Davidow LS, Davis JC, Peterson QP, Rubin LL, and Melton DA.** Reversal of beta cell de-differentiation by a small molecule inhibitor of the TGFbeta pathway. *eLife* 3: e02809, 2014.
8. **Bonner-Weir S and Orci L.** New perspectives on the microvasculature of the islets of Langerhans in the rat. *Diabetes* 31: 883-889, 1982.
9. **Braun M.** The somatostatin receptor in human pancreatic beta-cells. *Vitam Horm* 95: 165-193, 2014.
10. **Braun M, Ramracheya R, Amisten S, Bengtsson M, Moritoh Y, Zhang Q, Johnson PR, and Rorsman P.** Somatostatin release, electrical activity, membrane currents and exocytosis in human pancreatic delta cells. *Diabetologia* 52: 1566-1578, 2009.
11. **Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J, and Guillemin R.** Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science* 179: 77-79, 1973.
12. **Briant LJB, Reinbothe TM, Spiliotis I, Miranda C, Rodriguez B, and Rorsman P.** delta-cells and beta-cells are electrically coupled and regulate alpha-cell activity via somatostatin. *J Physiol* 596: 197-215, 2018.
13. **Brown M, Rivier J, and Vale W.** Biological activity of somatostatin and somatostatin analogs on inhibtion of arginine-induced insulin and glucagon release in the rat. *Endocrinology* 98: 336-343, 1976.
14. **Colturi TJ, Unger RH, and Feldman M.** Role of circulating somatostatin in regulation of gastric acid secretion, gastrin release, and islet cell function. Studies in healthy subjects and duodenal ulcer patients. *J Clin Invest* 74: 417-423, 1984.
15. **Cryer PE.** Hypoglycemia-Associated Autonomic Failure in Diabetes: Maladaptive, Adaptive, or Both? *Diabetes* 64: 2322-2323, 2015.
16. **Dean PM and Matthews EK.** Glucose-induced electrical activity in pancreatic islet cells. *J Physiol* 210: 255-264, 1970.

17. **Dezaki K, Damdindorj B, Sone H, Dyachok O, Tengholm A, Gylfe E, Kurashina T, Yoshida M, Kakei M, and Yada T.** Ghrelin attenuates cAMP-PKA signaling to evoke insulinostatic cascade in islet beta-cells. *Diabetes* 60: 2315-2324, 2011.
18. **Dezaki K, Hosoda H, Kakei M, Hashiguchi S, Watanabe M, Kangawa K, and Yada T.** Endogenous ghrelin in pancreatic islets restricts insulin release by attenuating Ca2+ signaling in beta-cells: implication in the glycemic control in rodents. *Diabetes* 53: 3142-3151, 2004.
19. **Diez JA, Arrojo EDR, Zheng X, Stelmashenko OV, Chua M, Rodriguez-Diaz R, Fukuda M, Kohler M, Leibiger I, Tun SBB, Ali Y, Augustine GJ, Barathi VA, and Berggren PO.** Pancreatic Islet Blood Flow Dynamics in Primates. *Cell reports* 20: 1490-1501, 2017.
20. **DiGruccio MR, Mawla AM, Donaldson CJ, Noguchi GM, Vaughan J, Cowing-Zitron C, van der Meulen T, and Huising MO.** Comprehensive alpha, beta and delta cell transcriptomes reveal that ghrelin selectively activates delta cells and promotes somatostatin release from pancreatic islets. *Mol Metab* 5: 449-458, 2016.
21. **Dubois MP.** Immunoreactive somatostatin is present in discrete cells of the endocrine pancreas. *Proc Natl Acad Sci U S A* 72: 1340-1343, 1975.
22. **Franklin I, Gromada J, Gjinovci A, Theander S, and Wollheim CB.** Beta-cell secretory products activate alpha-cell ATP-dependent potassium channels to inhibit glucagon release. *Diabetes* 54: 1808-1815, 2005.
23. **Gopel SO, Kanno T, Barg S, and Rorsman P.** Patch-clamp characterisation of somatostatin-secreting -cells in intact mouse pancreatic islets. *The Journal of physiology* 528: 497-507, 2000.
24. **Gromada J, Franklin I, and Wollheim CB.** Alpha-cells of the endocrine pancreas: 35 years of research but the enigma remains. *Endocrine reviews* 28: 84-116, 2007.
25. **Gutniak M, Grill V, Wiechel KL, and Efendic S.** Basal and meal-induced somatostatin-like immunoreactivity in healthy subjects and in IDDM and totally pancreatectomized patients. Effects of acute blood glucose normalization. *Diabetes* 36: 802-807, 1987.
26. **Hauge-Evans AC, King AJ, Carmignac D, Richardson CC, Robinson IC, Low MJ, Christie MR, Persaud SJ, and Jones PM.** Somatostatin secreted by islet delta-cells fulfills multiple roles as a paracrine regulator of islet function. *Diabetes* 58: 403-411, 2009.
27. **Head WS, Orseth ML, Nunemaker CS, Satin LS, Piston DW, and Benninger RK.** Connexin-36 gap junctions regulate in vivo first- and second-phase insulin secretion dynamics and glucose tolerance in the conscious mouse. *Diabetes* 61: 1700-1707, 2012.
28. **Hellman B, Salehi A, Grapengiesser E, and Gylfe E.** Isolated mouse islets respond to glucose with an initial peak of glucagon release followed by pulses of insulin and somatostatin in antisynchrony with glucagon. *Biochem Biophys Res Commun* 417: 1219-1223, 2012.
29. **Hellman B, Salehi A, Gylfe E, Dansk H, and Grapengiesser E.** Glucose generates coincident insulin and somatostatin pulses and antisynchronous glucagon pulses from human pancreatic islets. *Endocrinology* 150: 5334-5340, 2009.
30. **Henquin JC, Ibrahim MM, and Rahier J.** Insulin, glucagon and somatostatin stores in the pancreas of subjects with type-2 diabetes and their lean and obese non-diabetic controls. *Sci Rep* 7: 11015, 2017.
31. **Hoang DT, Hara M, and Jo J.** Design Principles of Pancreatic Islets: Glucose-Dependent Coordination of Hormone Pulses. *PLoS One* 11: e0152446, 2016.
32. **Hokfelt T, Efendic S, Hellerstrom C, Johansson O, Luft R, and Arimura A.** Cellular localization of somatostatin in endocrine-like cells and neurons of the rat with special references

to the A1-cells of the pancreatic islets and to the hypothalamus. *Acta Endocrinol Suppl (Copenh)* 200: 5-41, 1975.
33. **Huising MO, Pilbrow AP, Matsumoto M, van der Meulen T, Park H, Vaughan JM, Lee S, and Vale WW.** Glucocorticoids differentially regulate the expression of CRFR1 and CRFR2alpha in MIN6 insulinoma cells and rodent islets. *Endocrinology* 152: 138-150, 2011.
34. **Ipp E, Dobbs RE, Arimura A, Vale W, Harris V, and Unger RH.** Release of immunoreactive somatostatin from the pancreas in response to glucose, amino acids, pancreozymin-cholecystokinin, and tolbutamide. *J Clin Invest* 60: 760-765, 1977.
35. **Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi Y, Shinohara T, Hinuma S, Fujisawa Y, and Fujino M.** Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 422: 173-176, 2003.
36. **Korstanje R, Ryan JL, Savage HS, Lyons BL, Kane KG, and Sukoff Rizzo SJ.** Continuous Glucose Monitoring in Female NOD Mice Reveals Daily Rhythms and a Negative Correlation With Body Temperature. *Endocrinology* 158: 2707-2712, 2017.
37. **Kristinsson H, Bergsten P, and Sargsyan E.** Free fatty acid receptor 1 (FFAR1/GPR40) signaling affects insulin secretion by enhancing mitochondrial respiration during palmitate exposure. *Biochim Biophys Acta* 1853: 3248-3257, 2015.
38. **Kumar U, Sasi R, Suresh S, Patel A, Thangaraju M, Metrakos P, Patel SC, and Patel YC.** Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. *Diabetes* 48: 77-85, 1999.
39. **Lawlor N, George J, Bolisetty M, Kursawe R, Sun L, Sivakamasundari V, Kycia I, Robson P, and Stitzel ML.** Single-cell transcriptomes identify human islet cell signatures and reveal cell-type-specific expression changes in type 2 diabetes. *Genome Res* 27: 208-222, 2017.
40. **Li C, Chen P, Vaughan J, Lee KF, and Vale W.** Urocortin 3 regulates glucose-stimulated insulin secretion and energy homeostasis. *Proc Natl Acad Sci USA* 104: 4206-4211, 2007.
41. **Liu YJ, Vieira E, and Gylfe E.** A store-operated mechanism determines the activity of the electrically excitable glucagon-secreting pancreatic alpha-cell. *Cell calcium* 35: 357-365, 2004.
42. **Loud FB, Holst JJ, Egense E, Petersen B, and Christiansen J.** Is somatostatin a humoral regulator of the endocrine pancreas and gastric acid secretion in man? *Gut* 26: 445-449, 1985.
43. **MacDonald PE, De Marinis YZ, Ramracheya R, Salehi A, Ma X, Johnson PR, Cox R, Eliasson L, and Rorsman P.** A K ATP channel-dependent pathway within alpha cells regulates glucagon release from both rodent and human islets of Langerhans. *PLoS Biol* 5: e143, 2007.
44. **Menke A, Casagrande S, Geiss L, and Cowie CC.** Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. *JAMA : the journal of the American Medical Association* 314: 1021-1029, 2015.
45. **Merrins MJ, Poudel C, McKenna JP, Ha J, Sherman A, Bertram R, and Satin LS.** Phase Analysis of Metabolic Oscillations and Membrane Potential in Pancreatic Islet beta-Cells. *Biophysical journal* 110: 691-699, 2016.
46. **Murakami T, Fujita T, Miyake T, Ohtsuka A, Taguchi T, and Kikuta A.** The insulo-acinar portal and insulo-venous drainage systems in the pancreas of the mouse, dog, monkey and certain other animals: a scanning electron microscopic study of corrosion casts. *Arch Histol Cytol* 56: 127-147, 1993.

47. **Nadal A, Quesada I, and Soria B.** Homologous and heterologous asynchronicity between identified alpha-, beta- and delta-cells within intact islets of Langerhans in the mouse. *J Physiol* 517 (Pt 1): 85-93, 1999.
48. **Nyman LR, Ford E, Powers AC, and Piston DW.** Glucose-dependent blood flow dynamics in murine pancreatic islets in vivo. *Am J Physiol Endocrinol Metab* 298: E807-814, 2010.
49. **Ohtani O, Ushiki T, Kanazawa H, and Fujita T.** Microcirculation of the pancreas in the rat and rabbit with special reference to the insulo-acinar portal system and emissary vein of the islet. *Arch Histol Jpn* 49: 45-60, 1986.
50. **Patel YC.** Somatostatin and its receptor family. *Frontiers in neuroendocrinology* 20: 157-198, 1999.
51. **Portela-Gomes GM, Stridsberg M, Grimelius L, Rorstad O, and Janson ET.** Differential expression of the five somatostatin receptor subtypes in human benign and malignant insulinomas - predominance of receptor subtype 4. *Endocr Pathol* 18: 79-85, 2007.
52. **Rahier J, Goebbels RM, and Henquin JC.** Cellular composition of the human diabetic pancreas. *Diabetologia* 24: 366-371, 1983.
53. **Ravier MA and Rutter GA.** Glucose or insulin, but not zinc ions, inhibit glucagon secretion from mouse pancreatic alpha-cells. *Diabetes* 54: 1789-1797, 2005.
54. **Reimer MK, Pacini G, and Ahren B.** Dose-dependent inhibition by ghrelin of insulin secretion in the mouse. *Endocrinology* 144: 916-921, 2003.
55. **Reubi JC, Schaer JC, Wenger S, Hoeger C, Erchegyi J, Waser B, and Rivier J.** SST3-selective potent peptidic somatostatin receptor antagonists. *Proc Natl Acad Sci USA* 97: 13973-13978, 2000.
56. **Rivier J, Gulyas J, Kirby D, Low W, Perrin MH, Kunitake K, DiGruccio M, Vaughan J, Reubi JC, Waser B, Koerber SC, Martinez V, Wang L, Tache Y, and Vale W.** Potent and long-acting corticotropin releasing factor (CRF) receptor 2 selective peptide competitive antagonists. *Journal of medicinal chemistry* 45: 4737-4747, 2002.
57. **Rodriguez-Diaz R and Caicedo A.** Novel approaches to studying the role of innervation in the biology of pancreatic islets. *Endocrinology and metabolism clinics of North America* 42: 39-56, 2013.
58. **Rodriguez-Diaz R, Dando R, Jacques-Silva MC, Fachado A, Molina J, Abdulreda MH, Ricordi C, Roper SD, Berggren PO, and Caicedo A.** Alpha cells secrete acetylcholine as a non-neuronal paracrine signal priming beta cell function in humans. *Nature medicine* 17: 888-892, 2011.
59. **Rodriguez-Diaz R, Molano RD, Weitz JR, Abdulreda MH, Berman DM, Leibiger B, Leibiger IB, Kenyon NS, Ricordi C, Pileggi A, Caicedo A, and Berggren PO.** Paracrine Interactions within the Pancreatic Islet Determine the Glycemic Set Point. *Cell Metab* 27: 549-558 e544, 2018.
60. **Rorsman P, Berggren PO, Bokvist K, Ericson H, Mohler H, Ostenson CG, and Smith PA.** Glucose-inhibition of glucagon secretion involves activation of GABAA-receptor chloride channels. *Nature* 341: 233-236, 1989.
61. **Rorsman P and Braun M.** Regulation of insulin secretion in human pancreatic islets. *Annu Rev Physiol* 75: 155-179, 2013.
62. **Rorsman P and Huising MO.** The somatostatin-secreting pancreatic delta-cell in health and disease. *Nat Rev Endocrinol* 14: 404-414, 2018.

63. **Rui J, Deng S, Arazi A, Perdigoto AL, Liu Z, and Herold KC.** beta Cells that Resist Immunological Attack Develop during Progression of Autoimmune Diabetes in NOD Mice. *Cell Metab* 25: 727-738, 2017.
64. **Saito K, Yaginuma N, and Takahashi T.** Differential volumetry of A, B and D cells in the pancreatic islets of diabetic and nondiabetic subjects. *Tohoku J Exp Med* 129: 273-283, 1979.
65. **Salehi A, Qader SS, Grapengiesser E, and Hellman B.** Pulses of somatostatin release are slightly delayed compared with insulin and antisynchronous to glucagon. *Regulatory peptides* 144: 43-49, 2007.
66. **Samols E, Marri G, and Marks V.** Interrelationship of glucagon, insulin and glucose. The insulinogenic effect of glucagon. *Diabetes* 15: 855-866, 1966.
67. **Samols E, Marri G, and Marks V.** Promotion of Insulin Secretion by Glucagon. *Lancet* 2: 415-416, 1965.
68. **Samols E and Stagner JI.** Islet somatostatin--microvascular, paracrine, and pulsatile regulation. *Metabolism* 39: 55-60, 1990.
69. **Schauder P, McIntosh C, Arends J, Arnold R, Frerichs H, and Creutzfeldt W.** Somatostatin and insulin release from isolated rat pancreatic islets stimulated by glucose. *FEBS letters* 68: 225-227, 1976.
70. **Sosa-Pineda B, Chowdhury K, Torres M, Oliver G, and Gruss P.** The Pax4 gene is essential for differentiation of insulin-producing beta cells in the mammalian pancreas. *Nature* 386: 399-402, 1997.
71. **Stefan Y, Orci L, Malaisse-Lagae F, Perrelet A, Patel Y, and Unger RH.** Quantitation of endocrine cell content in the pancreas of nondiabetic and diabetic humans. *Diabetes* 31: 694-700, 1982.
72. **Stone VM, Dhayal S, Brocklehurst KJ, Lenaghan C, Sorhede Winzell M, Hammar M, Xu X, Smith DM, and Morgan NG.** GPR120 (FFAR4) is preferentially expressed in pancreatic delta cells and regulates somatostatin secretion from murine islets of Langerhans. *Diabetologia* 57: 1182-1191, 2014.
73. **Szkudelski T.** The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res* 50: 537-546, 2001.
74. **Taborsky GJ, Jr. and Ensinck JW.** Contribution of the pancreas to circulating somatostatin-like immunoreactivity in the normal dog. *J Clin Invest* 73: 216-223, 1984.
75. **Taborsky GJ, Jr. and Mundinger TO.** Minireview: The role of the autonomic nervous system in mediating the glucagon response to hypoglycemia. *Endocrinology* 153: 1055-1062, 2012.
76. **Tong J, Prigeon RL, Davis HW, Bidlingmaier M, Kahn SE, Cummings DE, Tschop MH, and D'Alessio D.** Ghrelin suppresses glucose-stimulated insulin secretion and deteriorates glucose tolerance in healthy humans. *Diabetes* 59: 2145-2151, 2010.
77. **Unger RH and Cherrington AD.** Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. *J Clin Invest* 122: 4-12, 2012.
78. **van der Meulen T, Donaldson CJ, Caceres E, Hunter AE, Cowing-Zitron C, Pound LD, Adams MW, Zembrzycki A, Grove KL, and Huising MO.** Urocortin3 mediates somatostatin-dependent negative feedback control of insulin secretion. *Nat Med* 21: 769-776, 2015.
79. **van der Meulen T, Xie R, Kelly OG, Vale WW, Sander M, and Huising MO.** Urocortin 3 marks mature human primary and embryonic stem cell-derived pancreatic alpha and beta cells. *PLoS One* 7: e52181, 2012.

80. **Vieira E, Salehi A, and Gylfe E.** Glucose inhibits glucagon secretion by a direct effect on mouse pancreatic alpha cells. *Diabetologia* 50: 370-379, 2007.
81. **Vierra NC, Dickerson MT, Jordan KL, Dadi PK, Kadare KA, Altman MK, Milian SC, and Jacobson DA.** TALK-1 reduces delta-cell endoplasmic reticulum and cytoplasmic calcium levels limiting somatostatin secretion. *Mol Metab* 9: 84-97, 2018.
82. **Walker JN, Ramracheya R, Zhang Q, Johnson PR, Braun M, and Rorsman P.** Regulation of glucagon secretion by glucose: paracrine, intrinsic or both? *Diabetes Obes Metab* 13 Suppl 1: 95-105, 2011.
83. **Wendt A, Birnir B, Buschard K, Gromada J, Salehi A, Sewing S, Rorsman P, and Braun M.** Glucose inhibition of glucagon secretion from rat alpha-cells is mediated by GABA released from neighboring beta-cells. *Diabetes* 53: 1038-1045, 2004.
84. **Yada T, Damdindorj B, Rita RS, Kurashina T, Ando A, Taguchi M, Koizumi M, Sone H, Nakata M, Kakei M, and Dezaki K.** Ghrelin signalling in beta-cells regulates insulin secretion and blood glucose. *Diabetes Obes Metab* 16 Suppl 1: 111-117, 2014.
85. **Zhang XD, Pechter D, Yang L, Ping X, Yao Z, Zhang R, Shen X, Li NX, Connick J, Nawrocki AR, Chakravarthy M, and Li C.** Decreased complexity of glucose dynamics preceding the onset of diabetes in mice and rats. *PLoS One* 12: e0182810, 2017.

Figure legends

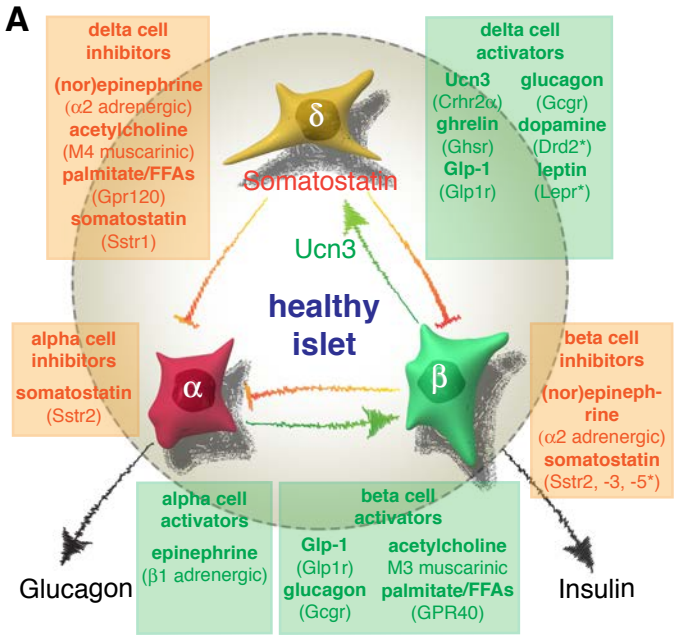
Figure 1: (A) Pancreatic delta cells receive input from numerous paracrine, endocrine and neural inputs and translate this into appropriate inhibition of glucagon and insulin release by alpha and beta cells. Select stimulatory and inhibitory inputs are given for each of the islet cell types. (B) Schematic representation of the profiles of insulin, glucagon and somatostatin secretion as a function of blood glucose.

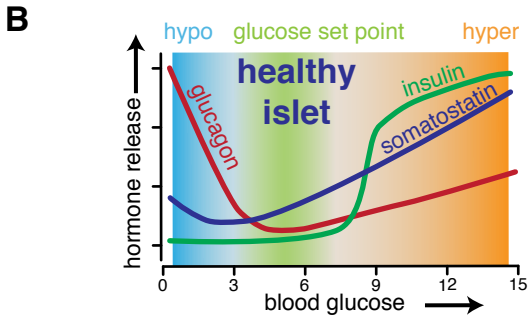
Figure 2: (A) Projection of a 3D reconstruction of a pancreatic islet from a transgenic reporter strain, captured by confocal microscope. Beta cells are visualized by the nuclear expression of an mCherry under control of the *Ins1* promoter. Delta cells are visualized by the expression of Cre recombinase under control of the somatostatin (*Sst*) promotor, which leads to their irreversible expression of yellow fluorescent protein (YFP; green). (B) Projection of a 3D reconstruction of a human pancreatic islet, captured by confocal microscope and stained for somatostatin (green), insulin (red) and glucagon (white). Nuclei (dapi) are counterstained in blue. Note how the human delta cells are notably more compact compared to the axon-like mouse delta cells. (C) The difference in morphology of mouse and human delta cells and beta cells from the same islet was quantified their circularity, defined as the normalized ratio of the area over the perimeter of the cell outline. Each cell outline was determined in Nikon Elements and circularity was calculated as 4 times π times the perimeter squared: (4*π*Area)/(Perimeter^(2)). A value of one indicates a perfect circle. Mouse delta cells stand out for their elongated morphology, which manifests as a significant reduction in circularity, compared to beta cells, while human delta cells are similarly compact to human beta cells. Numbers in-between parentheses reflect the number of cells

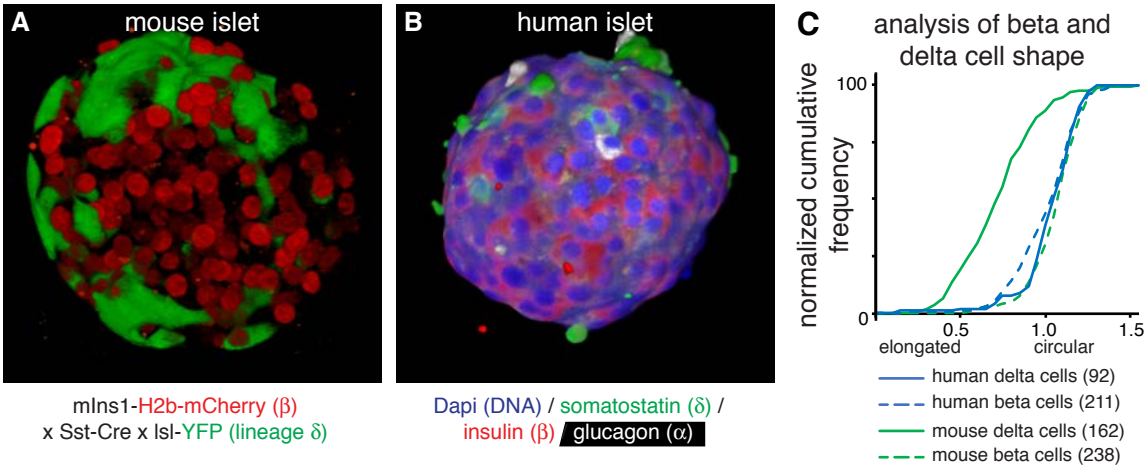
quantified from 3D confocal reconstructions of intact islets from two individual subjects for each species.

Figure 3: (A) In the absence of UCN3 in young neonatal mice, the homeostatic set point for glucose is determined by the balance between insulin and glucagon action. (B) After the onset of UCN3 expression in mouse beta cells, beta cell activation leads to the co-secretion of UCN3 with insulin. This activates feedback inhibition that curbs insulin secretion and effectively reduces insulin action.

Figure 4: (A) Model how tonic feedback inhibition on beta and alpha cells ensures the timely attenuation of insulin (or glucagon) secretion as glucose is restored to its homeostatic equilibrium. (B) When this local feedback breaks down, insulin secretion is des-inhibited. This prolongs insulin action, which causes glucose values to overshoot their glucose set point and contributes to hyperglycemia in diabetes.

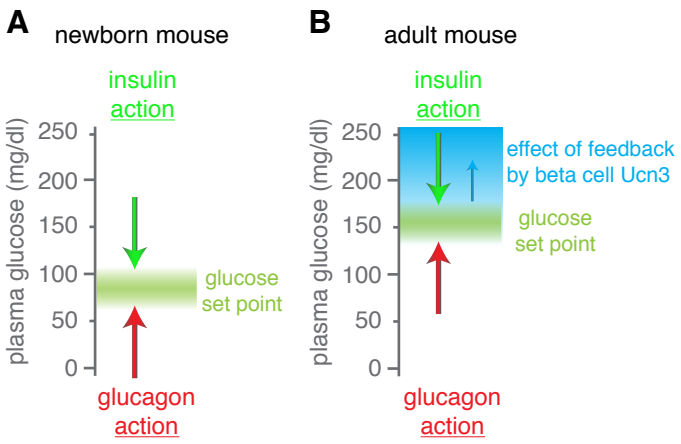

A
delta cell inhibitors
(nor)epinephrine
(α2 adrenergic)
acetylcholine
(M4 muscarinic)
palmitate/FFAs
(Gpr120)
somatostatin
(Sstr1)
delta cell activators
Ucn3
(Crhr2α)
glucagon
(Gcgr)
ghrelin
(Ghsr)
dopamine
(Drd2*)
Glp-1
(Glp1r)
leptin
(Lepr*)
δ
Somatostatin
Ucn3
healthy islet
alpha cell inhibitors
somatostatin
(Sstr2)
α
β
beta cell inhibitors
(nor)epineph-rine
(α2 adrenergic)
somatostatin
(Sstr2, -3, -5*)
alpha cell activators
epinephrine
(β1 adrenergic)
beta cell activators
Glp-1
(Glp1r)
acetylcholine
M3 muscarinic
glucagon
(Gcgr)
palmitate/FFAs
(GPR40)
Glucagon
Insulin

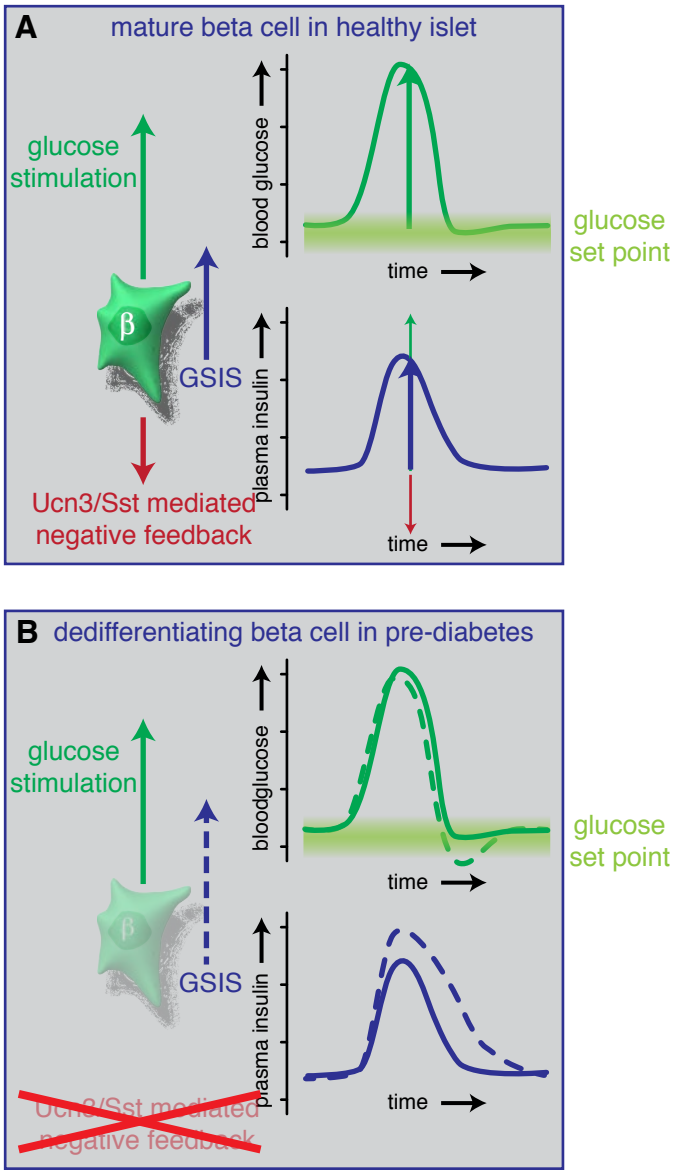

B
hypo
glucose set point
hyper
healthy islet
glucagon
insulin
somatostatin
hormone release
0
3
6
9
12
15
blood glucose



mIns1-H2b-mCherry (β)
x Sst-Cre x lsl-YFP (lineage δ)

Dapi (DNA) / somatostatin (δ) /
insulin (β) glucagon (α)


A
newborn mouse
insulin
action
plasma glucose (mg/dl)
250
200
150
100
50
0
glucose
set point
glucagon
action
B
adult mouse
insulin
action
plasma glucose (mg/dl)
250
200
150
100
50
0
effect of feedback
by beta cell Ucn3
glucose
set point
glucagon
action


A
mature beta cell in healthy islet
glucose
stimulation
β
GSIS
Ucn3/Sst mediated
negative feedback
blood glucose
time
plasma insulin
time
glucose
set point
B
dedifferentiating beta cell in pre-diabetes
glucose
stimulation
β
GSIS
bloodglucose
time
plasma insulin
time
glucose
set point