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REVIEW

Paracrine and autocrine control of insulin secretion in human islets: evidence and pending questions

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Abstract

Insulin secretion by β-cells is largely controlled by circulating nutrients, hormones, and neurotransmitters. However, recent years have witnessed the multiplication of studies investigating whether local regulation also takes place within pancreatic islets, in which β-cells cohabit with several other cell types. The cell composition and architectural organization of human islets differ from those of rodent islets and are particularly favorable to cellular interactions. An impressive number of hormonal (glucagon, glucagon-like peptide-1, somatostatin, etc.) and nonhormonal products (ATP, acetylcholine, γ-aminobutyric acid, dopamine, etc.) are released by islet cells and have been implicated in a local control of insulin secretion. This review analyzes reports directly testing paracrine and autocrine control of insulin secretion in isolated human islets. Many of these studies were designed on background information collected in rodent islets. However, the perspective of the review is not to highlight species similarities or specificities but to contrast established and speculative mechanisms in human islets. It will be shown that the current evidence is convincing only for a minority of candidates for a paracrine function whereas arguments supporting a physiological role of others do not stand up to scrutiny. Several pending questions await further investigation.

glucagon; human islet; insulin secretion; paracrine and autocrine control; somatostatin

INTRODUCTION

Tight quantitative and temporal control of insulin secretion by pancreatic β-cells is crucial for metabolic homeostasis, in particular the stability of blood glucose. This control is largely achieved by circulating nutrients, hormones, and neurotransmitters. However, local regulation may also take place within islets, in which β-cells cohabit with several other cell types. The hypothesis that insulin secretion is under control of products released by islet β-cells or nonβ-cells was raised several decades ago (61) and extensively investigated during recent years. In theory, hormones secreted by islet cells are capable of exerting a direct influence on insulin secretion in one of two ways. They could operate systemically as circulating endocrine signals that reach all β-cells, on which they would act at lower concentrations than those expected to occur locally, just after their release within the islet interstitium. Alternatively, islet hormones and nonhormonal products could exert a local, paracrine action if they were not immediately washed away by blood flow and could reach their cognate receptors at the β-cell surface, either after a very short trip in islet capillaries or by diffusion within the islet intercellular space. This type of action obviously depends on the islet architecture and on the relative proportion and proximity of different cell types.

For decades, rodent islets were the best model to study β-cell physiology. However, despite many phenotypic and functional similarities, substantial differences between species (31, 67, 73) accelerated resort to human islets (31, 33, 50). That switch was particularly relevant to obtain a reliable picture of paracrine interactions, because the cell composition and organization of human and rodent islets are different (6, 10, 13). Besides β-cells (~50–60%), human islets also contain ~25–35% α-cells secreting glucagon, ~7–10% δ-cells secreting somatostatin, and a few ε-cells secreting ghrelin (13, 59). Islets from the small lobe located at the posterior face of the head contain pancreatic polypeptide cells instead of α-cells (51, 63). In humans, the structural organization of the islets is characterized by a close proximity of the three main cell types, which favors local reciprocal influences to a greater extent than in rodents (6, 10, 20).

Since human islets are not readily amenable to genetic manipulations, in vitro studies testing whether insulin secretion is subject to paracrine control first ascertain that the suspected paracrine signal is indeed released by islet cells and then rely on its immunoneutralization or degradation and on blockage of its receptors. Changes in insulin secretion then support a local action. On the other hand, preventing degradation of the putative signal in isolated islets artificially increases its concentration and shows that a local action is possible but is not sufficient to establish physiological relevance. This caveat is particularly important for correct interpretation of static experiments, during which products released from islet cells can accumulate in the incubation

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medium and diffuse into the interstitial space rather than being cleared by blood flow in situ. The problem is minimized but not suppressed when islets are perifused at a sufficiently high flow rate. It remains uncertain whether the flux of perifusion medium through the islet interstitium adequately reproduces blood flow. The optimal model of intact perfused human pancreas is no longer used and was only rarely employed to investigate paracrine control of insulin secretion (12, 43, 75).

Here, I have critically analyzed publications reporting experiments directly testing paracrine control of insulin secretion in isolated human islets. Many of these investigations were based on background information collected in rodents. However, the perspective of this review is not to highlight species similarities or specificities but to contrast established and speculative mechanisms in human islets. Comparisons with studies using rodent islets can be found in reviews with a different focus (9, 38, 41, 57, 67). As it is obvious that products released by a given β-cell within an islet may act on both the very same cell (autocrine effect) and on its cognate neighbors (paracrine effect), the term autocrine will refer to the same cell type, not the same cell. Paracrine control is generally viewed as the direct modulation of β-cell function by one type of nonβ-cells, but indirect mechanisms sequentially involving two types of nonβ-cells may also operate. In recent years, an astonishingly large number of factors released by islet cells have been considered as putative autocrine or paracrine regulators of insulin secretion in human islets (Fig. 1), but only a few meet the criteria to qualify.

PARACRINE AND AUTOCRINE ACTIONS OF ISLET HORMONES IN β-CELLS

Insulin

Proinsulin processing in β-cells yields insulin and C-peptide, which are costored within granules and released together. Measuring C-peptide secretion, therefore, makes it possible to evaluate the possible influence of insulin on its own secretion. It is generally agreed that the fall in plasma C-peptide occurring during isoglycemic hyperinsulinemic clamps is neurally mediated (64). In vitro, application of huge concentrations of exogenous insulin to incubated or perifused islets failed to provide convincing evidence for a direct feedback (62, 64). Surprisingly, however, an autocrine action of insulin on β-cells has not been directly tested in isolated islets. Measurements of C-peptide secretion after immunoneutralization of insulin have not been published. Two studies using an insulin receptor antagonist to evaluate glucagon and somatostatin secretion did not report insulin secretion data (24, 85).

Islet Amyloid Polypeptide

Islet amyloid polypeptide (IAPP) is synthesized in β-cells, stored in granules, and secreted with, but in much lower amounts (~1%), than insulin (58, 91). No study ever reported acute effects of IAPP on insulin secretion or evidence for an autocrine action in human β-cells.

Somatostatin

Somatostatin (SST) exists in two forms. SST28 is secreted by the gut, whereas SST14 is secreted by δ-cells in the stomach and islets. In blood, over 95% is SST28, and its concentration varies between 5 and 50 pM (17). In vitro, perfusing human pancreases (43) or incubating islets (72, 76, 91) with nanomolar concentrations of exogenous SST14 or SST28 consistently inhibited insulin secretion during stimulation with 4–20 mM glucose (G4–G20). SST secretion by pancreatic δ-cells is stimulated by glucose (11) and occurs at a rate 1–2% that of insulin (32, 86), similar to the relative contents of the two hormones in whole pancreases (36). To test whether islet SST exerts local effects, whole pancreases were perfused with anti-SST monoclonal antibody, with the expectation that neutralization of the inhibitory factor would be followed by an increase in insulin secretion. In a first study, such an increase occurred during retrograde perfusion, not during

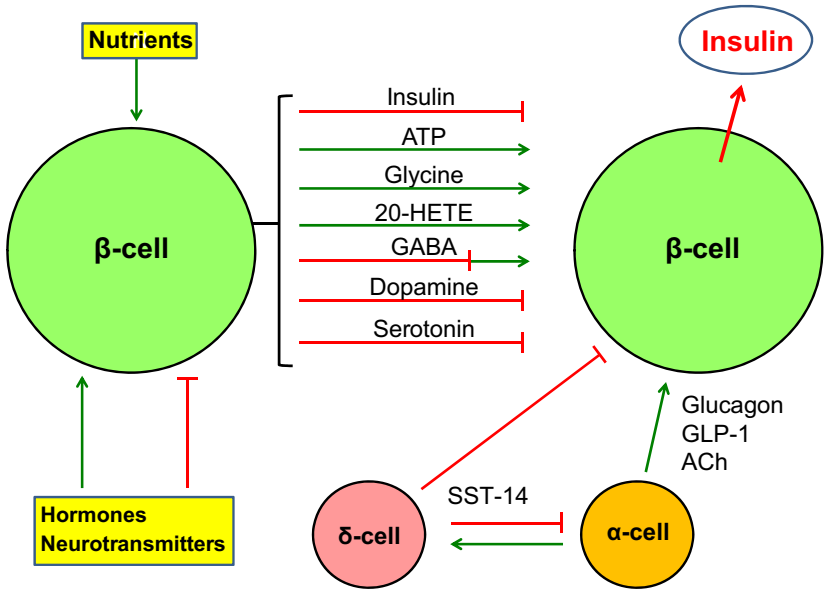

Figure 1. Proposed mediators of the paracrine and autocrine control of insulin secretion in human islets.

normal anterograde perfusion of the organ (75). This paradox prompted the suggestion that β-cells are perfused before δ-cells, an interpretation that has been seriously challenged by recent reconstructions of the islet microcirculation (21). In a larger study, an increase in insulin secretion occurred during normal anterograde perfusion of anti-SST antibodies (43). However, SST can also reach a fraction of β-cells via the cytoplasmic extensions of δ-cells (3, 29) and, perhaps, a greater number by diffusion in the intercellular space (38). Paracrine control by δ-cells could also be indirect, with primary inhibition of α-cells by SST (72) and secondary attenuation of a positive action of the latter on insulin secretion.

Although these routes theoretically permit paracrine inhibition of insulin secretion, this hypothesis has never been directly tested in isolated human islets. Two studies using the same antagonist of SST receptors to assess paracrine inhibition of α-cells by δ-cells have yielded controversial results. Glucagon secretion was unaffected in G1 (24, 86) but strongly increased (24) or unchanged (86) by the antagonist in the presence of inhibitory concentrations of glucose. No insulin data were reported. Insulin secretion was tested in the simultaneous presence of antagonists of SST receptors and exogenous SST (72, 91), not in islets stimulated with glucose alone when only local SST could have been active. Whether the relatively rare δ-cells exert a direct or indirect paracrine control of β-cells in human islets remains, therefore, an open question.

Glucagon and Glucagon-Like Peptide-1

Glucagon and glucagon-like peptide-1 (GLP-1) derive from a common precursor, proglucagon (56). Both are produced by α-cells, but the main sources of GLP-1 are L cells of the ileum and colon, from which it is released during meals to serve as an incretin hormone. The half-life of its active form GLP-1(7–36) is short because of rapid degradation by the widely distributed dipeptidyl-peptidase-4 (DPP4), so that its plasma concentration is lower than that of glucagon (56). It is generally agreed that human pancreases and isolated islets contain much less GLP-1 than glucagon (2–8%) (37, 74, 82, 92). Inexplicably, two studies measured higher proportions of islet GLP-1 (25–50%) and reported stimulation (52) or inhibition (23) of its release by high glucose during incubations without DPP4 inhibitor. No influence of glucose on GLP-1 secretion was observed during islet culture with a DPP4 inhibitor (60, 69, 92). Further studies would be welcome to make precise the relative contents and secretion rates of the two hormones in the same isolated islets and to establish whether GLP-1 secretion parallels that of glucagon in response to different glucose concentrations. Dissociations might reflect secretion of the two proglucagon peptides by distinct α-cells (15). Notwithstanding these uncertainties, paracrine actions of glucagon and GLP-1 on β-cells are plausible.

In human β-cells, GLP-1 receptors (GLP1R) are about twice more expressed than glucagon receptors (GCGR) (67). At physiological plasma concentrations (<50 pM), each ligand specifically binds to its cognate receptor, but glucagon is also able to activate GLP1R at nanomolar concentrations, whereas GLP-1 does not act on GCGR (77). In the presence of G10, 10 nM glucagon increased insulin secretion, and its effect was suppressed by antagonists of GCGR (16, 39). GLP-1 was also consistently, although variably, effective at 1–100 nM (22, 25, 39, 49) and remarkably at physiological 1 pM in G6 (70). Its effects were suppressed by exendin-9, an antagonist of GLP1R.

The existence of paracrine control of insulin secretion by α-cells has been evaluated for each hormone individually or in combination (Table 1). Contrary to expectations, immunoneutralization of glucagon inexplicably increased insulin secretion in pancreases perfused with G4 and G12 (12). In contrast, an antagonist of GCGR diminished glucose-induced insulin secretion in islets incubated in the absence of exogenous glucagon (39). This inhibition was confirmed recently with newer antagonists (66) or an antibody against the receptor (16). The agreement is less complete concerning the effects in low glucose (G3). Two studies found no impact of GCGR antagonists (39, 66), whereas a third one reported a marked decrease (16). Six laboratories evaluated whether exendin-9 affects insulin secretion in the absence of exogenous GLP-1 or glucagon (Table 1). Two of these reported no effect (52, 70), whereas the other four observed a 30–50% decrease of insulin secretion in high glucose (15, 16, 18, 94). When both GLP1R and GCGR were antagonized simultaneously, the response to G10 was unsurprisingly inhibited (16), but the effects in lower glucose were paradoxical. An unexplained doubling of insulin secretion occurred in G3 + amino acids (94), whereas secretion was abolished in G3 alone (16). Although inhibition in G3 is compatible with the mild stimulation of human β-cells under these conditions (34), its magnitude (~85%) is puzzling.

DPP4 is present in islets (15, 60, 69). Its inhibition by a gliptin augmented the local concentration of GLP-1 secreted by α-cells (15, 52, 60), which was anticipated to unmask a paracrine stimulatory action. However, acute treatment with a gliptin did not affect (15, 30) or only marginally increased insulin secretion (60), except in relatively poorly responsive islets (92). As the concentration of gliptins used in these studies was within the therapeutic range, it appears that intraislet effects of DPP4 inhibitors are functionally modest, which suggests that their therapeutic benefits are unlikely to depend on protection of GLP-1 secreted by α-cells.

Overall, the results are compatible with the hypothesis that α-cells exert a positive paracrine action on β-cells through glucagon and perhaps GLP-1. Given that insulin secretion increases when glucagon secretion decreases, the action must be tonic rather than acute. Whether it reflects maintenance of sufficient levels of cAMP, as in rodent β-cells, could be assessed by verifying that blockage of GCGR and GLP1R in human islets is no longer inhibitory in the presence of a clamped concentration of cAMP.

Ghrelin

Circulating ghrelin mainly originates from the stomach, but the gene is also expressed in other tissues including islet ε-cells (89). To become active, ghrelin must be acetylated. Both its receptor and the acetylating enzyme have been identified in islets (28), thus making paracrine actions plausible. At 100 nM (500× higher than in plasma) ghrelin did not affect insulin secretion by islets incubated in G3 but decreased their response to G17 by 30% (48). Notably, expression of the

Table 1. *Paracrine control of insulin secretion by glucagon and GLP-1 in human islets*

First Author and Year	*n*	Method	Test Conditions	Effect of Test Agent	SI Glucose		Ref.
Huypens 2000	8	Inc 2 h	Antag GCGR in G3 and G10	None in G3 and 0.6× in G10	G10/G3	4.2×	39
Rodriguez-Diaz 2018	4	Peri ? min	Antag GCGR in G3 and G7	None in G3 and 0.8× in G7	?	?	66
Capozzi 2019	3	Peri 24 min	Antag GCGR in G3 and G10	0.6× in G3 and 0.8× in G10	G10/G3	11×	16
		Peri 24 min	Ex-9 in G3 and G10	0.5× in G3 and 0.5× in G10			
		Peri 30 min	Ex-9 + Antag GCGR	0.2× in G3 and 0.5× in G10			
Zhu 2019	3	Peri 30 min	Ex-9 in G3 and G17 (+AA)	None in G3 and 0.7× in G17	G17/G3	4.3×	94
			Ex-9 + Antag GCGR	2.5× in G3 + AA			
Marchetti 2012	3	Inc 45 min	Ex-9 in G3 and G11	None	G11/G3	2.3×	52
Shigeto 2015	2	Inc 1 h	Ex-9 in G6	None	G6/G1	2.2×	70
De Souza 2020	4	Inc 1 h	Ex-9 in G15	0.5×	G15/G3	7.0×	18
Campbell 2020	3	Peri 50 min	Ex-9 in G3 and G11	None in G3 and 0.7× in G17	G11/G3	2.8×	15
	6	Peri 50 min	Sitagliptin 200 nM	None in G3 and G11	G11/G3	3.4×	
Zhang 2017	5	Inc 1 h	Linagliptin 5 nM in G3-G25	None in G3 and 1.8× in G25	G25/G3	1.9×	92
Omar 2014	4	Inc 2 h	Vildagliptin 500 nM in G17	1.2×	G17/G3	3.0×	60
Guida 2018	?	Inc 1 h	Sitagliptin 100 nM in G20	None	G20/G1	4.2×	30

AA, amino acids; Antag GCGR, antagonist of glucagon receptor; Ex-9, exendin-9 (antagonist of GLP-1 receptor); gliptins, inhibitors of GLP-1 degradation by DPP4; Inc, incubation; *n*, number of islet preparations used in reported experiments; Peri, perifusion; SI glucose, stimulation index of glucose = ratio of insulin secretion at the indicated glucose concentrations (G in mM) in the same study.

ghrelin receptor is minimal in β- compared with δ-cells (67), and ghrelin stimulates somatostatin secretion in incubated islets (19). It is therefore theoretically possible that the changes in insulin secretion observed in vitro are indirect. However, the rarity of ε-cells in islets is hardly compatible with a paracrine control.

Pancreatic Polypeptide

Pancreatic polypeptide (PP) is produced by F cells, which are rare (<1%) in the vast majority of islets except in those within the small "ventral lobe" located at the posterior face of the pancreatic head (the name "ventral lobe" stems from its embryological origin, not its anatomic positioning). The other peculiarity of these islets is their poverty in α-cells (9, 51, 63). The receptor of PP (PPYR1) is present in α-cells but not in β-cells (2), and no test of possible effects of PP on insulin secretion has been reported. Interestingly, an overlooked study compared insulin secretion in islets isolated separately from the two lobes and measured a greater stimulation index of glucose in islets from the main lobe than from the PP-rich lobe (4.7× vs. 2.2×) (84). Although hormone contents of the islets were unfortunately not available, the stronger response of islets from the main lobe (those that all laboratories isolate and study) can most likely be attributed to the paracrine action of α-cells.

PARACRINE AND AUTOCRINE ACTIONS OF ISLET NONHORMONAL PRODUCTS IN β-CELLS

ATP

ATP and ADP are present in insulin granules and released when the hormone is secreted. Human β-cells express both ionotropic purinergic receptors P2X and metabotropic P2Y receptors. Their subtypes, transduction pathways, and relative sensitivities to ADP and ATP have been discussed elsewhere (67). ATP itself was tested in only one study. Short pulses of ATP increased insulin secretion with a similar efficacy in G3 and G11, and the effects were prevented by an antagonist of P2X receptors (40). In contrast, the effects of ATP on glucagon secretion were negligible (40). In longer islet incubations, synthetic agonists of ATP increased insulin secretion whether they acted on P2X or P2Y receptors (4, 26, 27). These experiments thus showed that purinergic signaling amplifies β-cell secretory function (Table 2). To test whether ATP released from β-cells is involved in an autocrine control, islets were challenged by glucose alone in the presence of purinergic receptor antagonists. Antagonists of P2X receptors decreased the insulin response to glucose (27, 40), whereas the inhibitory effect of P2Y antagonists was inconsistent (40, 42).

The concentration of nucleotides in the extracellular space is controlled by integral plasma membrane enzymes, the ectonucleotidases that degrade ATP into ADP and AMP. All cell types of human islets express the NTPDase-3 isoform (46), and this expression is much greater than in any other tissue (79). Inhibition of ectonucleotidases to protect ATP consistently increased insulin secretion. However, in two studies, the effect was seen in the presence of stimulatory glucose (4, 79), whereas it was present in G3 only in a third study (40). Conversely, destroying ATP with apyrase modestly (15%) reduced glucose-induced insulin secretion in one study (40) but not in another (4). This set of data is not consistent (Table 2). It is difficult to understand how ATP protection was stimulatory whereas ATP degradation was ineffective in G8 (4), whereas ATP protection was ineffective and ATP degradation inhibitory in G11 (40). Even more puzzling is the contrast between a doubling of insulin secretion by ATP protection and the lack of effect of ATP degradation in G3 (40).

In summary, autocrine control of human β-cells through ATP is possible but not decisively established. Alternatively, the intriguing abundance of ectonucleotidases in human islets might be viewed as a way to prevent such an autocrine action.

γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the central nervous system (7). Human β-cells contain five times more GABA than insulin (88), and its fractional release is 20 times greater (87). High glucose does not stimulate GABA release, which occurs by

Table 2. *Autocrine and paracrine control of insulin secretion by ATP and GABA in human islets*

First Author and Year	*n*	Method	Test Conditions	Effect of Test Agent	SI Glucose		Ref.
ATP							
Jacques 2010	3	Peri 10 min	ATP in G3 and G11	1.6× in G3 and G11	G11/G3	8.0×	40
			Antag P2X and P2Y in G11	0.5× (P2X) and None (P2Y)			
			ATP protection	2.0× in G3 and None in G11			
			ATP degradation	None in G3 and 0.85× in G11			
Fernandez 2001	2	Inc 1.5 h	Ago P2X in G3 and G8	1.4× in G3 and 3.6× in G8	G8/G3	1.5×	26
			Ago P2Y in G3 and G8	None in G3 and 3.0× in G8			
Glas 2009	3	Inc 1 h	Ago P2X in G5	2.3×	G11/G5	2.0×	27
			Antag P2X in G5 and G11	None in G5 and 0.6× in G11			
Khan 2019	14	Inc 1 h	Antag P2Y in G1 and G10	None in G1 and 0.6× in G10	G10/G1	7.0×	42
Bartley 2019	6	Inc 1 h	Ago P2Y in G8	1.4×	G8/G3	2.4×	4
	2	Inc 1 h	ATP protection in G8	2.7×	G8/G3	1.6×	
			ATP degradation in G8	None			
Syed 2013	6	Inc 1 h	ATP protection	None in G3 and 1.8× in G11	G11/G3	1.8×	79
GABA							
Korol 2018	10	Inc 0.5 h	GABA 0.1 μM in G20	1.6×	?	?	44
Braun 2010	7	Inc 1 h	GABA-A Antag in G3 - G20	0.5× in G6 and None in G3,G10,G20	G20/G1	5.2×	8
Taneera 2012	5	Inc 1 h	GABA-A Antag in G1 and G17	None	G17/G1	9.0×	80
			GABA-B Antag in G1 and G17	None in G1 and 1.5× in G17			
Menegaz 2019	3	Peri 5 min	GABA 10 μM in G5	0.6×			54
		Peri 10 min	Inhibitor GABA synthesis	None in G3 and 1.6× in G11	G11/G3	2.3×	

Ago, agonist, Antag: antagonist; GABA-A and GABA-B, GABA receptors; *n*, number of islet preparations used in reported experiments; Inc, incubation; SI glucose, stimulation index of glucose = ratio of insulin secretion at the indicated glucose concentrations (G in mM) in the same study; Peri, perifusion; P2X and P2Y, purinergic receptors.

diffusion through volume-regulated channels (54), but it lowers its cytosolic concentration through switches in metabolic pathways (87). β-Cells possess both stimulatory ionotropic GABA-A receptors and inhibitory metabotropic GABA-B receptors, the latter being by far the more abundant (67).

At 10 μM, exogenous GABA inhibited insulin secretion in islets perifused with G5 (54), but at 0.1 μM it stimulated secretion in islets incubated with G20 (44) (Table 2). Strangely, the same study reported that GABA was inhibitory when exocytosis was measured by electrophysiological techniques in single cells. Blockage of GABA-A receptors impaired the insulin response to G6 (8) but had no effect with G3, G10, and G20 (8, 80). Nonetheless, this restricted inhibitory effect led to the speculation that β-cell-derived GABA exerts an autocrine-positive effect on insulin secretion via GABA-A receptors. Blockage of GABA-B receptors augmented the response to G20 (80), suggesting that they mediate a negative autocrine action of GABA.

Indirect approaches tested the consequences of changes in GABA production and release. Inhibiting GABA synthesis in β-cells with 10 mM allylglycine almost immediately increased insulin secretion (54), but the effect was so rapid that depolarization by allylglycine entry is an alternative explanation. Slowing intracellular catabolism of GABA augmented its cellular content and accelerated its efflux but variably caused rapid inhibition of insulin secretion (54) or no change over 24 h (87). Finally, glutamine is known to increase GABA formation and release but does not inhibit insulin secretion (16). Because of all these contradictions and uncertainties, it cannot be taken for granted that β-cell GABA plays an autocrine role in insulin secretion.

Glutamate

The negatively charged amino acid glutamate is present in plasma at concentrations of 50–100 μM. In the central nervous system, which is protected from circulating glutamate by the blood-brain barrier, the amino acid acts as an excitatory neurotransmitter on three types of ionotropic receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), Kainate, and *N*-methyl-D-aspartate (NMDA) (93). These receptors are also expressed in human β-cells in proportions that vary between studies (14, 67). Exactly how glutamate is transported across the β-cell membrane and whether its transport affects the membrane potential are unclear (67).

Observations that glutamate is released from α-cells when ambient glucose decreases (14), and perhaps from β-cells when glucose increases, raised the possibility that the amino acid acts as a paracrine signal in islets. Adding inhibitors of NMDA receptors to incubated islets tended to increase insulin secretion in G2 and considerably (50–100%) augmented the effect of G20, which prompted the speculation that stimulated β-cells activate their own brake (53). In contrast, short activation (5 min) of each of the three receptors failed to change insulin secretion in islets perifused in G1–G11 despite the concomitant increase in glucagon secretion (14). In summary, the picture remains blurry, with little evidence that glutamate originating from islet cells could exert a paracrine control of β-cells in the presence of blood-derived glutamate.

Glycine

Like glutamate, glycine is present at a much lower concentration in cerebral fluid than in plasma (~5 vs. ~250 μM), which permits the amino acid to act as a neurotransmitter on ionotropic glycine receptors, especially in the spinal cord and brain stem (7). These receptors are expressed in human β-cells (67) but should be continuously desensitized by blood-derived glycine. However, it has been suggested that the interstitial concentration of glycine in islets is kept low because β-cells take up the amino acid and store it within

vesicles. Upon stimulation and rise in cytosolic [Ca^{2+}], glycine would then be released and serve as a positive autocrine signal for insulin secretion (90). The hypothesis is supported by a slight augmentation (1.3×) of insulin secretion by 800 μM exogenous glycine in islets incubated in G6 and by a strangely large (40%) decrease of the response to G10 by strychnine, a blocker of glycine receptors (90). Observations from another study speak against the hypothesis: high glucose did not change the islet content of glycine, 500 μM exogenous glycine did not affect insulin secretion, and strychnine did not alter the response to G10 (47). The question remains open.

Acetylcholine

Exogenous acetylcholine (ACh) increases insulin secretion in human islets (55, 65, 95). Classic models hold that the neurotransmitter is released by parasympathetic nerve endings and activates muscarinic M3 receptors in β-cells. However, one study reported that most α-cells contain ACh vesicles that are released when ambient glucose decreases and proposed that this local production mediates a delayed positive paracrine control of insulin secretion (65). The ability of physostigmine, a blocker of ACh degradation by acetylcholinesterase, to double insulin secretion in G3 supports the hypothesis that ACh present in islets may exert a tonic effect in β-cells. However, blockage of muscarinic receptors by atropine also increased insulin secretion under the same conditions (55). This contradiction forced those authors to implicate stimulation of somatostatin secretion by ACh with secondary inhibition of β-cells in their complex model (55, 65). In addition, if such a control were operative, a positive allosteric modulator of M3 receptors should increase insulin secretion in the absence of exogenous ACh. This was not the case; such a modulator had the expected effect only when added with exogenous ACh (95). Finally, not all studies agree on the presence of ACh vesicles in α-cells (81). Because of these conflicting findings, it is prudent to conclude that a paracrine action of α-cells through release of ACh is not convincingly established.

Dopamine

β-Cells synthesize dopamine from blood-derived tyrosine, store it in secretory vesicles, and release it with insulin in response to glucose stimulation (71). Dopamine type 2 receptors (D2R) are present in islets, and their activation by dopamine or synthetic agonists inhibits glucose-induced insulin secretion (68, 71). An inhibitor of dopamine accumulation within insulin granules and antagonists of D2R increased insulin secretion in islets incubated with G8–G15 alone (71). These convergent findings prompted the suggestion that dopamine release, concurrently with insulin, represents an autocrine inhibitory regulation (71). However, it is puzzling that mere inhibition of D2R, which are mainly localized at the granule membrane and become operative only when exposed to the extracellular milieu during exocytosis (68, 71), can triple insulin secretion, especially since only few exocytotic events occur in individual β-cells during glucose stimulation (35).

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is produced in β-cells and released in response to glucose stimulation (1, 5). In the absence of exogenous serotonin, glucose-induced insulin secretion was increased by an agonist of 5HT2 receptors and completely suppressed by blockage of the receptors (5). Exogenous serotonin was tested at concentrations exceeding that reached by endogenous serotonin in the islet interstitium. In islets incubated with G16, inhibition of insulin secretion mediated by 5HT1 receptors was observed (5, 71). In islets perifused with G11, no change in insulin secretion was detected, whereas secretion of glucagon and somatostatin was markedly inhibited (1). Overall, these somewhat discordant results do not support an autocrine role of serotonin in insulin secretion.

20-Hydroxyeicosatetraenoic Acid

Synthesis and release of 20-hydroxyeicosatetraenoic acid (20-HETE), a metabolite of arachidonic acid, increase in glucose-stimulated islets (83). Exogenous 20-HETE was found to augment insulin secretion no less than three- to fourfold in G2 and G16, and this effect was suppressed by an antagonist of the fatty acid receptor FFAR1. The antagonist and an inhibitor of 20-HETE synthesis reduced glucose-induced insulin secretion by 30%. These observations led to the suggestion that 20-HETE production and release by β-cells constitute a positive autocrine control of insulin secretion (83). In contrast, several antagonists of FFAR1 were without effect on insulin secretion in incubated or cultured islets in other studies (45, 78). The contradiction can probably be explained by the fact that islets were incubated in a very small volume (20 μL) to allow accumulation of putatively active products in the first study (83), whereas, in the other two, such products were diluted in larger volumes, as they would be by blood flow in vivo. Overall, the autocrine effect of 20-HETE is doubtful.

CONCLUSIONS

Pancreatic β-cells adjust insulin production to a plethora of signals extrinsic to the islets, mainly circulating nutrients and hormones, but a local intraislet control may also be important for an optimal response. The least one can say is that there is no shortage of candidates to operate as paracrine or autocrine regulators of insulin secretion. It is implausible that normal β-cells need so many local levels of control and even doubtful that they can achieve harmonious integration of so many, sometimes contradictory, signals. The strongest evidence is the positive paracrine action of α-cells, which clearly involves glucagon, whereas the contribution of GLP-1 needs additional proof. The inhibitory role of δ-cells still requires direct demonstration. The implication of other candidate signals remains hypothetical. Further experiments are necessary to validate or disprove these hypotheses. I hope that the issues raised in this review will be useful in designing convincing tests, but I am not sure that isolated islets devoid of microcirculation are the optimal model to obtain convincing answers that can indisputably be translated to the in vivo situation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

J.-C.H. drafted manuscript, prepared figures and tables, and wrote and approved final version of manuscript.

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