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Inter-organ communication and regulation of beta cell function

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Abstract

The physiologically predominant signal for pancreatic beta cells to secrete insulin is glucose. While circulating glucose levels and beta cell glucose metabolism regulate the amount of released insulin, additional signals emanating from other tissues and from neighbouring islet endocrine cells modulate beta cell function. To this end, each individual beta cell can be viewed as a sensor of a multitude of stimuli that are integrated to determine the extent of glucose-dependent insulin release. This review discusses recent advances in our understanding of inter-organ communications that regulate beta cell insulin release in response to elevated glucose levels.

Keywords

Beta cell; Decretin; Ghrelin; Galanin; Incretin; Insulin; Inter-organ; Islet; Leptin; Muscarinic; Review; Xenin-25

Intestine to beta cell communication

Incretin hormones

The incretin hormones glucagon-like peptide 1 (GLP-1) (1–4) and glucose-dependent insulinotropic polypeptide (GIP, also known as gastric inhibitory polypeptide) are among the most widely studied modulators of beta cell function (5–8).

GLP-1—GLP-1, a proteolytic product of pre-proglucagon, which is synthesised and secreted from intestinal L cells upon stimulation by intestinal nutrients, is released into the circulation shortly after meal intake, increasing circulating GLP-1 levels. At the endocrine pancreas, through binding to its cognate stimulatory G protein ($G_{\alpha s}$)-coupled receptor (GLP-1R), it suppresses alpha cell glucagon secretion and potentiates insulin secretion from

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beta cells in a glucose-dependent manner. It is important to note that GLP-1 action on beta cells only occurs when the circulating glucose level is above a certain threshold, which in humans lies in the low normoglycaemic range. In the presence of elevated glucose levels, beta cell GLP-1R stimulation results in a more pronounced rise in intracellular calcium, and the frequency and number of insulin vesicles exocytosed (i.e. insulin secretion) is increased. GLP-1 is rapidly degraded enzymatically by dipeptidyl peptidase IV (DPP-IV) located in the endothelium, rendering the biological half-life of GLP-1 shorter than 5 min (9)

The above-described concept of GLP-1–GLP-1R action is successfully exploited by diabetes pharmacotherapy, with GLP-1R agonists or DPP-IV inhibitors that both augment GLP-1 action in beta cells and increase insulin secretion in patients with type 2 diabetes mellitus. In general, in type 2 diabetic patients, the meal-induced increase in circulating GLP-1 levels is similar to that observed in non-diabetic individuals; however, it is not as effective in potentiating insulin secretion. The underlying reasons for this remain incompletely understood (9). Experimental findings suggest that signals external to beta cells inhibit the beta cell response to incretin action (see below) and that, at least in humans with a prolonged history of type 2 diabetes, a beta cell autonomous defective response to GLP-1 is demonstrable during experimental studies on isolated islets, attributable to the loss of key beta cell-defining transcription factors (10).

Recent studies using sophisticated genetic mouse models have provided new insights into the physiological and pharmacological mechanisms of GLP-1 action. Mouse models of conditional, tissue-specific GLP-1R ablation (11) indicate that the presence of GLP-1R on beta cells is not necessary for physiological (not during diabetes and insulin resistance) GLP-1 action in modulating beta cell function, and suggest the possibility that GLP-1R activation in afferent neurons located in the intestine or portal venous vasculature may relay GLP-1 action indirectly via neuronal mechanisms to beta cells (11). Selective beta cell ablation of GLP-1R in mice did not alter insulin secretion or glucose tolerance during oral or intraperitoneal glucose tolerance tests, while systemic treatment of these mice with a pharmacological GLP-1R agonist did result in the absence of insulin secretion potentiation. The investigators of these studies concluded that, under physiological conditions, incretin action through GLP-1R is independent of the presence of GLP-1R on beta cells, and that the effects of GLP-1 may be mediated via non-endocrine mechanisms. These findings raise the possibility that in type 2 diabetes the absence of incretin action may not be solely due to the diminished response of beta cells to GLP-1, but, rather, may be due to disruptions in neuronal relay mechanisms between the intestine and the endocrine pancreas (11).

In addition to GLP-1, L cells synthesise and secrete other endocrine hormones that may influence beta cell function. In the rat, the epithelium of the proximal portion of the intestine contains L cells that produce cholecystokinin (CCK) and neurotensin, while distally localised L cells express peptide YY (PYY) (12).

GIP and xenin-25—In contrast to GLP-1 agonist treatment, pharmacological administration of GIP fails to augment glucose-stimulated insulin secretion (GSIS) in humans with type 2 diabetes. The mechanisms of action of GIP, which is secreted from intestinal epithelial K cells, as an incretin hormone appear to be more complex than those of

GLP-1. Importantly, a second protein, called xenin-25, is co-synthesised and secreted from K cells (13). Mice selectively lacking K cells exhibit a blunted response to exogenous GIP replacement, and in vivo co-administration of xenin-25 restores GIP incretin action (13). In vitro studies on xenin-25 and GIP treatment of mouse islets indicate that xenin-25 does not act directly on beta cells. Rather, xenin-25 acts by stimulating cholinergic signalling to beta cells via non-ganglionic circuitry that, to date, remains to be characterised (14).

Co-administration of xenin-25 with GIP potentiates GSIS in non-diabetic people but not in individuals with established type 2 diabetes. However, co-treatment with recombinant xenin-25 and GIP reduces postprandial glycemia by delaying gastric emptying in humans with or without type 2 diabetes (15). Thus, while GIP is considered an incretin hormone, its mechanisms of action and its significance in glucoregulation remain to be fully understood. Importantly, establishing why combined recombinant xenin-25/GIP treatment is ineffective in type 2 diabetic patients may further our understanding of beta cell failure in type 2 diabetes.

Furthermore, studies in mice lacking GIP (as opposed to lacking K cells, described above) suggest a wider role for GIP in metabolic control. Absence of GIP production in mice, slightly impairs GSIS and glucose tolerance. However, when placed on a high-fat content diet, the absence of GIP protects against obesity and insulin resistance and maintains increased fatty acid oxidation (16).

More recently, studies of GIP receptor (GIPR) ablation specifically in mouse beta cells (17) reveal at least two signalling pathways that are engaged by GIPR activation in beta cells. The first is the well-known activation of cyclic AMP (cAMP) production, the second is the extracellular signal-regulated kinase (ERK)-dependent pathway. GIPR–ERK but not cAMP-dependent signalling in beta cells stimulates the expression of T cell-specific transcription factor-1 (TCF1), which is encoded by *Tcf7* (17). Mice lacking GIPR specifically in beta cells exhibit normal glucose tolerance, while glucose-stimulated insulin secretion is slightly dampened. Interestingly, the response to GLP-1R activation in GIPR-ablated islets is augmented, suggesting potential compensatory mechanisms that maintain insulin secretion in the absence of GIPR signalling.

Importantly, *Tcf7* levels are lower in islets of diabetic mice and in humans with type 2 diabetes, and $Tcf7^{-/-}$ mice exhibit increased susceptibility to apoptotic injury and glucose intolerance with aging or during increased metabolic demand in the fact of high fat content diet feeding (17) The antiapoptotic actions in beta cells of TCF1 are likely to be mediated by the TCF7 target pituitary tumour-transforming gene 1 (*Pttg1*), which encodes securin, a protein involved in DNA repair and chromosome stabilising mechanisms. Thus, a GLP-1R-independent, GIPR–ERK–TCF1–PTTG1 axis is proposed to exert protective and antiapoptotic effects on beta cells (17).

Decretin hormones

Neuromedin U—While the incretin hormones stimulate increased insulin release from beta cells in the feeding state, prolonged nutrient deprivation and fasting are accompanied by reduced insulin secretion (i.e. ‘fasting diabetes’) (18). This dampened insulin secretion is

not readily reversed by i.v. glucose supply, arguing against a simple absence of nutrients (i.e. glucose) and for an active suppression of beta cell insulin secretion as a regulatory mechanism of beta cell function during periods of nutrient deprivation (17). Such observations have propagated the concept of decretin hormones that act during fasting to regulate in a manner inverse to that of incretins.

Indeed, using a nutrition-deprived *Drosophila melanogaster* model, limostatin was found to be upregulated in gut-associated endocrine cells and to suppress secretion from *Drosophila* insulin-like peptide-producing cells by interacting with the *Drosophila* orthologue of the inhibitory neuromedin U receptor (NMUR) (19). NMUR1 is a G protein-coupled receptor that, in mammals, mediates the peripheral actions of NMU. It can be localised to human beta cells, and in perifusion assays of human islets, NMU suppresses GSIS. Furthermore, in humans, NMU expression is detectable in foregut-derived stomach and duodenum, and its immunoreactivity is localised to chromogranin B-positive enteroendocrine cells in the duodenal epithelium (19). Circulating NMU concentrations during fasting and feeding have not been reported to date. Although it is unclear whether NMU fulfils this classical criterion of a bone fide hormone, NMU appears to possess all the other properties expected of a decretin (19).

Remarkably, an NMU variant, NMU R165W, which in humans confers autosomal-dominant early-onset obesity, fails to suppress GSIS in perifusion studies, suggesting a sequential pathogenic link between increased insulin secretion followed by increased risk of obesity in humans (19).

Ghrelin and galanin—Ghrelin and galanin are two more hormones that are synthesised and secreted from the gastrointestinal tract and suppress beta cell glucose responsiveness. Ghrelin is produced in foregut-derived stomach epithelium and also in endocrine cells located in the pancreatic islet (epsilon cells) (20–22). Specific post-translational acylation by ghrelin *O*-acyltransferase (GOAT) is required for ghrelin to bind to and activate its receptor (23). Fasting induces ghrelin expression in both stomach epithelium and the central nervous system. Circulating acyl-ghrelin levels increase during nutritional deprivation. Furthermore, acyl-ghrelin potently inhibits GSIS in vivo in mice and in cultured islets in vitro via interaction with the ghrelin receptor. Ghrelin-deficient mice are less protected from fasting-induced hypoglycaemia (24, 25). Collectively, these findings indicate that ghrelin may function as a fasting-induced hormone, exerting, among other effects, homeostatic effects that serve to suppress insulin secretion and protect against hypoglycaemia. Furthermore, specific pharmacological inhibition of GOAT, an enzyme with the exclusive function of activating ghrelin function, results in increased in vivo insulin secretion and improved glucose homeostasis in animal models of diet-induced obesity and glucose intolerance (26).

Galanin is expressed in neuronal and intestinal tissue and, in vitro, suppresses GSIS from isolated rodent islets. The regulation of galanin secretion and the mechanisms by which it regulates insulin secretion in humans remain unknown. In experimental systems, it is likely that galanin inhibits insulin secretion via interaction with a G protein-coupled receptor that signals through Gα(o2) (27, 28).

Liver to beta cell communication

Hyperglucagonaemia has long been recognised as a hallmark of type 2 diabetes. Furthermore, subsets of individuals who are at risk for developing type 2 diabetes (i.e. first-degree relatives of patients with type 2 diabetes) also exhibit relative hyperglucagonemia. The mechanistic link between hyperglucagonemia and defective insulin secretion in type 2 diabetes has recently been elucidated using genetic mouse models (29). Glucagon acts on a relatively small number of target cells and orchestrates processes that protect against or aid recovery from hypoglycaemia. In the liver, glucagon binds to its $G_{\alpha s}$-coupled receptor to stimulate cyclic AMP (cAMP) synthesis, which in turn binds to the regulatory subunit of protein kinase A (PKA) holoenzyme, thereby releasing and activating the catalytic subunit of PKA. Subsequent downstream signalling results in glucose mobilisation from glycogen stores and transcriptional upregulation and activation of the gluconeogenesis program (29).

As expected, transgenic hepatocyte-specific overexpression of the catalytic subunit of PKA in mice results in the upregulation of the transcriptional gluconeogenesis program and in hyperglycaemia. However, insulin secretion remains insufficient to adequately control glycaemia. Similarly, selective ablation of the gene encoding PKA regulatory subunit 1a (*Prkar1a*) in hepatocytes also results in increased hepatic glucose production and insulin secretion insufficient to control blood glucose levels (29). Mice from the latter study harboured a factor in their circulation that inhibited insulin secretion from mouse islets cultured in vitro. Gene expression analysis of livers from mice with ablated *Prkar1a* surprisingly revealed the peptide hormone kisspeptin 1 to be upregulated, which in turn resulted in elevated circulating kisspeptin 1 levels (30).

The kisspeptin 1 receptor (Kiss1R) is present in abundance on pancreatic beta cells, and acute kisspeptin 1 treatment of mice causes impaired glucose tolerance owing to dampened GSIS. Kiss1R is related to the galanin and ghrelin receptors, and similar to galanin and ghrelin, kisspeptin 1 binds to its cognate receptor and inhibits cAMP production in beta cells, thereby dampening GSIS (30). Moreover, mouse models of diabetes mellitus, such as the high-fat content diet-fed mouse or the *db*/*db* mouse, exhibit elevated liver kisspeptin 1 production and impaired glucose tolerance. Kisspeptin 1 knockdown in the liver of these animal models ameliorates glucose tolerance and increases GSIS. Importantly, humans with diabetes also exhibit increased liver kisspeptin 1 production and circulating kisspeptin 1 levels. Human islets express Kiss1R, and it is likely that, as in the mouse model, kisspeptin 1 would impair GSIS from human islets (30).

In summary, a tri-hormonal glucoregulatory endocrine circuit exists between the pancreatic islet and the hepatocyte. Glucagon stimulates gluconeogenesis in the liver, which raises glucose levels and stimulates kisspeptin 1 production, which in turn suppresses insulin secretion.

Adipocyte to beta cell communication

Leptin, a hormone produced by adipocytes, suppresses insulin secretion. Pancreatic beta cells express the functional long form of the leptin receptor (ObRb), and isolated islets incubated in vitro with leptin exhibit reduced GSIS (31–36). Furthermore, in mice,

conditional genetic ablation (using the Cre–LoxP system) of ObRb specifically in pancreatic beta cells is accompanied by augmented GSIS in vivo. These studies suggest that leptin acts directly on pancreatic beta cells to impair insulin secretion. The findings have recently been reexamined in light of observations that the transgene carrying Cre recombinase under the control of the rat insulin promoter is also expressed ectopically in areas of the brain where the leptin receptor is also expressed. More recent studies using a different mouse model of beta cell-specific Cre expression while avoiding neuronal Cre expression, suggest that the in vivo effects of leptin may not be mediated via its receptor on beta cells (37). Nevertheless, as outlined in the section below on the skeletal system, leptin may regulate beta cell function indirectly at least in the mouse by controlling bone mass and osteocalcin production.

Adiponectin is another major adipose tissue-derived hormone. In addition to facilitating beta cell proliferation and regeneration in mice after in vivo experimental ablation, it has recently been shown to modulate beta cell lipid metabolism, thereby protecting beta cells from lipotoxicity and preserving beta cell function (38, 39). Further studies related to adiponectin receptors are anticipated to elucidate how adiponectin exerts these effects on beta cells.

Other products secreted by adipocytes, such as resistin and fibroblast growth factor 21 (FGF21), have been proposed to regulate beta cell function (reviewed in (40)). However, there are currently insufficient data on these adipocyte-derived products to allow for any clear conclusions as to whether these effects occur via direct action on beta cells or indirectly via changes in other metabolically relevant tissues (40)

Skeletal system to beta cell communication

Bone

Bone is increasingly being recognised as an endocrine tissue that participates in regulating whole body fuel metabolism and glucoregulation. Teleologically, the role of the skeleton as a prerequisite for transitioning from marine to terrestrial existence and locomotion would posit adaptive processes for metabolic homeostasis (41).

Osteocalcin—In terms of the skeletal compartment, osteocalcin has in recent years emerged as an important regulator of beta cell functional mass, insulin sensitivity and peripheral tissue fuel combustion, as well as male fertility (42, 43). Osteocalcin, one of the most abundant components of bone extracellular matrix is synthesised and secreted by osteoblasts. Osteocalcin undergoes post-translational carboxylation on glutamic residues. Formation of undercarboxylated osteocalcin (Glu-OCN) or resorption of bone through osteoclasts, yielding Glu-OCN, releases undercarboxlated osteocalcin into the circulation, allowing it to reach target tissues and act through the osteocalcin receptor (44). Observations from osteocalcin knockout mice indicate that osteocalcin plays a role in regulating beta cell mass and function (45, 46). Osteocalcin knockout mice exhibit low beta cell mass and impaired glucose tolerance owing in part to impaired GSIS and to insulin resistance in peripheral tissue. Moreover, osteocalcin treatment in mice increases beta cell mass and insulin secretion, improves glucose homoeostasis and prevents the development of type 2 diabetes (45). Furthermore, mice lacking the presumptive osteocalcin receptor GPRC6A (a

$G_{\alpha s}$ protein-coupled receptor) specifically on beta cells exhibit impaired beta cell proliferation, insulin synthesis and GSIS (47).

Remarkably, osteoblasts, which synthesise osteocalcin, express insulin receptors, and insulin stimulates osteocalcin production. Mice with an osteoblast-specific lack of insulin receptors show reduced bone density, reduced circulating osteocalcin levels and reduced beta cell mass, impaired GSIS and glucose tolerance. Conversely, overexpression of insulin receptors in osteoblasts improves glucose tolerance in mice on a diabetogenic high-fat diet (HFD). These findings suggest a feed-forward interplay between insulin-producing beta cells and osteoblasts, osteoclasts and bone turnover (48, 49).

More recently, delta-like 1 (DLK-1) has been proposed to counteract the effects of insulin on osteoblasts, providing a counter-regulatory mechanism to the feed-forward loop between osteocalcin and insulin. Osteocalcin stimulates DLK-1 production in beta cells, from where DLK-1 is co-secreted with insulin. In turn, DLK-1 inhibits insulin receptor signalling in osteoblasts (50).

Leptin and adiponectin—Leptin, originating from adipocytes, which are an osteocalcin target, acts via the hypothalamus and the sympathetic nervous system to inhibit bone formation (51, 52). This, in turn, results in reduced circulating (undercarboxylated) osteocalcin, followed by reduced insulin secretion (as outlined above). While these early results on the regulation of bone mass by leptin are very convincing, recent studies suggest that leptin action in the brain may increase rather than decrease bone mass (53). Adiponectin, another adipose tissue product, also participates in the regulation of bone mass and osteocalcin production. Adiponectin has opposing effects on bone mass. It directly causes osteoblast apoptosis, but via hypothalamic action reduces sympathetic tone and counteracts the effects of leptin on bone mass (54).

While these observations on the complex relationship between bone and fuel homeostasis were based on mouse model studies, much work remains to be done to evaluate the broader significance of these findings in humans in this exciting field. Osteoprotegerin (OPGN), recently shown to regulate beta cell proliferation, will be discussed further below (55).

Skeletal muscle

A signalling pathway from the skeletal muscle to the pancreatic islet has been described in rodent models. In mice subjected to exercise in spinning wheels, skeletal muscle produces IL-6, which reaches pancreatic alpha cells via the circulation and, via its cognate receptor, modulates post-translational processing of pro-glucagon to favour the production of GLP-1 rather than glucagon. In turn, GLP-1 release from alpha cells potentiates GSIS in neighbouring beta cells (56). Thus, muscle exercise is reported to modulate beta cell function indirectly via IL-6 originating from skeletal muscle, altering pro-glucagon processing in alpha cells, and exposing beta cells to higher GLP-1 concentrations (56).

Based on these observations, it is conceivable that exercise not only alters insulin sensitivity but also influences beta cell function and insulin secretion. Whether these mechanisms described in rodents also apply to humans is at present unclear, but is important to establish

as this may further our understanding of the pathogenesis of metabolic disease associated with infrequent exercise and have implications for its treatment. Furthermore, recent in vitro studies suggest a role for additional myotube-derived factors (‘myokines’) that influence beta cell function. These myokines are differentially expressed in normal vs insulin-resistant myotubes and appear to act through mitogen-activated protein 4 kinase 4 signalling (57).

Gonads to beta cell communication

The main gonadal sex steroids testosterone (58, 59)and oestrogen (60) have been reported to protect pancreatic beta cells from damaging insults such as glucotoxicity or streptozotocin-induced oxidative stress. In humans, oestrogen replacement in menopausal women reduces the incidence of diabetes mellitus. At the molecular level, oestrogen is shown to directly act on beta cells to exert prosurvival effects and increase insulin synthesis via oestrogen response element (ERE)-independent extranuclear oestrogen receptors ERα, ERβ and through the G protein-coupled oestrogen receptor (60–66).’

In male mice with selective ablation of the androgen receptor in beta cells GSIS is impaired, leading to reduced glucose tolerance (67). These mice are also less capable of compensating for diet-induced insulin resistance compared with controls, and islets isolated from these mice exhibit reduced GSIS in vitro, similar to AR antagonist (flutamide)-treated human islets (67). Collectively, these observations suggest that the androgen receptor physiologically regulates beta cell function in male mice. More detailed work using genetic mouse models will be required to elucidate at a molecular level the role for the androgen receptor and male sex steroids on beta cell function and survival.

Placenta to beta cell communication

Metabolism changes during pregnancy to meet the maternal and fetal energy requirements. Circulating levels of both prolactin and human placental lactogen are elevated to counteract pregnancy-related insulin resistance and to regulate functional beta cell mass.

In mice, the tyrosine hydroxylase genes *Tph1* and *Tph2*, encoding isoforms of the rate-limiting enzyme for serotonin (5-hydroxytryptamine, 5-HT), are upregulated in beta cells during pregnancy. Serotonin synthesis is upregulated in the beta cells of pregnant mice and, in an autocrine/paracrine fashion, serotonin binds to cognate $G_{q/11}$-coupled $5\text{-}HT_{2B}$ receptors to stimulate beta cell proliferation (68). Through binding to the $5\text{-}HT_3$ receptor, serotonin also reduces the resting membrane potential of beta cells and the threshold for GSIS (55, 69). Both prolactin and placental lactogen, acting through the prolactin receptor, stimulate tyrosine hydroxylase, establishing this endocrine regulatory communication between the placenta and the beta cell. Activated prolactin receptor signalling in beta cells also stimulates the production and release of osteoprotegerin (OPGN), a protein that binds to and inhibits the receptor activator of NF-κB (RANK) ligand (RANKL). RANKL inhibits beta cell proliferation, and its sequestration by OPGN thus releases the brake on beta cell proliferation. This mechanism has been confirmed both in mouse and human islets. Thus, this second mechanism engaged by the prolactin receptor during pregnancy serves to regulate functional beta cell mass (55). It is important to note that the placenta produces large amounts of kisspeptin 1 (70), which would be expected to impair beta cell function and

insulin secretion. The interplay between kisspeptin 1 and prolactin signalling on beta cells has not been experimentally examined.

In summary, beta cells can be viewed as sensors that constantly receive signals from a variety of peripheral tissues. These signals, which could have opposing effects, fluctuate according to the metabolic state of the source tissues. Upon reaching beta cells, they are integrated and modulate insulin secretion in response to the predominant physiological stimulus, namely, glucose. How nutrients and metabolites, such as fatty acids and their metabolic derivatives, amino acids and metabolic products originating from other tissues and from microbiota, interplay with and participate in inter-organ signalling and in regulating beta cell function is beyond the scope of this review and deserves a separate dedicated review.

Central nervous system regulation of beta cell function

Pancreatic beta cells are innervated by the autonomic nervous system. Studies in humans and in rodents following vagotomy have reported reduced GSIS, suggesting that parasympathetic innervation supports beta cell function ([71] and references therein). Other studies suggest that vagal innervation may also control beta cell proliferation and mass; and the ventromedial hypothalamus may negatively regulate vagus-relayed signalling in beta cell proliferation (72–75). Recent reports indicate that, in contrast to rodent islets, human islets are innervated primarily by cholinergic neurons, suggesting that sympathetic islet innervation may be relevant in rodents but not humans (76). Furthermore, in humans, alpha cells may also be an additional source of acetylcholine, which acts on beta cells in a paracrine fashion (77).

Several neurotransmitters released from peripheral autonomic nerves have been proposed to modulate GSIS, including the principal parasympathetic neurotransmitter acetylcholine (71, 78, 79). The G_q protein-coupled muscarinic M_3 acetylcholine receptor (M3R; but not M1R or M2R) subtype is expressed at high density on mouse pancreatic beta cells (80), and beta cell-specific M3R knockout results in impaired GSIS in mice (81). Furthermore, beta cell-specific pharmacological activation of this receptor via a M3R–Gq-signalling-coupled designer receptor exclusively activated by designer drug (DREADD) potentiates GSIS, and after chronic stimulation also stimulates beta cell proliferation (82). Despite these observations and the identification of brain nuclei that regulate metabolic controls, such as insulin sensitivity and hepatic glucose production (83) and hunger, satiety and food-intake (84), distinct brain regions/nuclei, which regulate betacell function through vagal innervation and, potentially, via targeting M3R signalling on beta cells have thus far not been described. Furthermore, in addition to acetylcholine, parasympathetic neuronal endings in the pancreas release a multitude of other neurotransmitters (71). It remains unclear whether hypothalamic signals relayed by the vagus that modulate beta cell function act directly via beta cell muscarinic receptors or indirectly via cholinergic stimulation of an intermediary ganglion, from where secondary efferent neurotransmission is relayed to the beta cell.

The sympathoadrenal and adrenergic innervation of islets modulates insulin secretion in rodents, while its role in humans remains unclear. Chemical sympathectomy results in decreased basal and glucose-stimulated insulin levels in mice but not in rats (85). Adrenalectomy also results in reduced basal insulin levels in mice, suggesting that not only sympathetic innervation but also circulating adrenal hormones modulate beta cell function (85). More recently, genetic mouse models with defined ablation of adrenergic signalling in islets was reported to result in disturbed islet architecture and functional maturation of beta cells (86).

Furthermore, galanin, which is abundantly expressed in neuroendocrine in the intestinal tract and also in neuronal endings surrounding the islets of Langerhans, suppresses glucose-stimulated insulin (26, 87) (see above).

Central unresolved questions

From this overview it is clear that many important aspects of how beta cell function is regulated remain unanswered. There are likely to be additional signals involved in regulating beta cell function that will be revealed. With these anticipated advances the following central and enduring questions will need to be revisited as this research field moves forward:

1. How translatable are observations on inter-organ regulation of beta cell function made in experimental mouse models to the situation in human (patho-)physiology?
2. What is the hierarchy among the different stimuli that modulate beta cell insulin secretion?
3. Can impaired beta cell function in type 2 diabetes mellitus be sub-classified into groups of beta cell autonomous and non-beta cell autonomous downregulation of glucose-dependent insulin release?

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Abbreviations

DLK-1	Delta-like 1
DPP-IV	Dipeptidyl peptidase IV
ERK	Extracellular signal-regulated kinase
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide 1
GOAT	Ghrelin *O*-acyltransferase
GSIS	Glucose-stimulated insulin secretion

M3R	M_3 acetylcholine receptor
NMUR	Neuromedin U receptor
TCF1	T cell-specific transcription factor-1
PYY	Peptide YY

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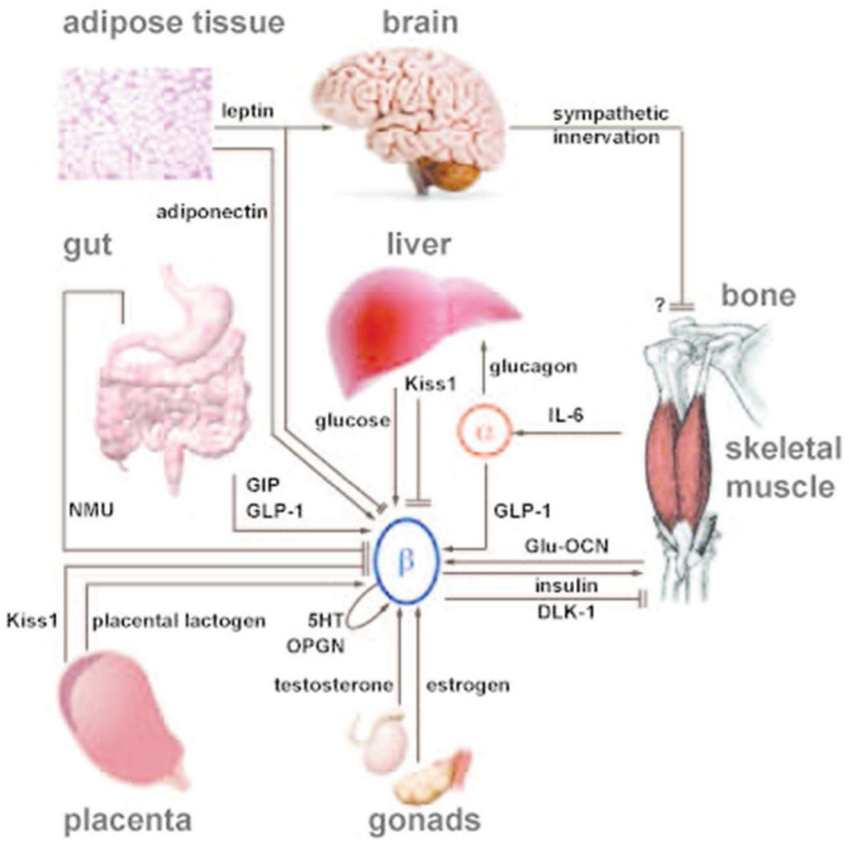

Fig. 1.

Inter-organ communication pathways influencing beta cell function. The figure depicts the current understanding of principal inter-tissue signalling pathways that modulate GSIS from pancreatic beta cells. Signals modulate beta cell function in both positive (arrows) and negative (double bars) directions. The individual pathways are described in the main text. α, alpha cell; β, beta cell; Glu-OCN, Glu-OCN, undercarboxlated osteocalcin