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G-protein coupled receptors controlling pancreatic β-cell functional mass for the treatment of Type 2 Diabetes

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Abstract

The first phase of insulin secretion is altered during the early stages of diabetes and is followed by progressive loss of the ability of glucose to stimulate insulin secretion. The primary causes of insulin-secretory defects are still unknown. Better understanding of the signaling pathways linked to the activation of G-protein coupled receptors (GPCRs), and their mutual interactions in the β-cells remains crucial. This represents a prerequisite for any strategy to develop therapeutic tools that aim to modulate the insulin-secretory function and/or mass of β-cells. This review summarizes knowledge over the last two years on GPCRs functionally expressed in β-cells, which present key features for the development of therapy for type 2 diabetes.

Keywords

G-protein coupled receptor, Pancreatic β-cell, Insulin secretion, Diabetes, Therapeutic strategies, Signal transduction

Introduction

Type 2 diabetes (T2D) is a serious health problem that affects million people worldwide **[1]**. The pathophysiology of T2D is characterized by insulin resistance and progressive impairment of β-cell function. The insulin resistance of T2D, although important for its pathophysiology, is not sufficient to establish the disease unless major deficiency of β-cell function co-exists **[2]**. Reduced β-cell mass has also been proposed to be associated with T2D **[3]**. Therefore, innovative therapeutic strategies aiming at preserving β-cell function and survival are of great interest to slow the progression or even to prevent T2D **[4, 5]**. β-cell dysfunction and death are caused by multiple stressors including chronic hyperglycemia (glucotoxicity), lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, the formation of amyloid deposits, and proinflammatory cytokines **[6]**. Unfortunately, none of the currently and widely prescribed antidiabetic drugs favor the maintenance of endogenous functional β-cell mass, revealing an unmet medical need.

In vivo, the insulin secretion is triggered by the circulating nutrients, mainly by the glucose **[7, 8]**. Glucose triggers insulin secretion when it is taken up into the β-cell through the glucose transporter 2 (GLUT2). When glucose is metabolized, the ATP/ADP ratio is increased. This results in the closure of the ATP-sensitive potassium channels and membrane depolarization which favors the opening of the voltage-gated calcium channels increasing the calcium influx within the β-cell. Elevation of the calcium concentration in the cytosol triggers insulin secretion (Figure 1) **[8]**. The glucose-induced insulin secretion is radically modulated in terms of amplitude by many factors such as hormones, growth factors, or neurotransmitters, the majority of which acts by activation or inhibition of intracellular signaling pathways engaged by seven membrane-spanning G-protein coupled receptors (GPCRs) or tyrosine kinase receptors. Activation of GPCRs results in different β-cell signaling, involving the cAMP/protein kinase A (PKA)/Epac, and the inositol triphosphate (IP_3)/diacylglycerol (DAG) pathways, as well as changes in protein phosphorylation and protein acylation. The cAMP/PKA and the IP_3/DAG pathways engaged during the activation of GPCRs are among the most important signaling pathways for the β-cell biology (Figure 1). Gαs mediates increases in intracellular cAMP associated with increased insulin secretion, while Gαi mediates decreases in intracellular cAMP and inhibition of insulin secretion. Gαq mediates increases in IP_3 and DAG production through the activation of phospholipase C (PLC) associated with increased release of calcium (Ca^{2+}) for the ER and enhanced insulin secretion **[9, 10]**. GPCRs control the dynamics of the exocytosis of insulin granules, to maintain the state of differentiation, and to regulate the β-cell survival programs **[9]**. Table 1 presents the GPCRs expressed in β-cells (in bold the GPCRs covered in this review).

GLP-1 receptor

Specific glucagon like peptide-1 (GLP-1) receptors (GLP-1R) are coupled to Gαs with subsequent activation of adenylate cyclase and elevation of cAMP levels in β-cells. When activated, GLP-1R potentiates glucose-induced insulin secretion through cAMP production. GLP-1R is a key target for T2D treatment **[11]**.

Beyond Gαs coupling to cAMP production, GLP-1R undergoes agonist-mediated endocytosis. Over the last two years, the consequences of modulating GLP-1R endocytic trafficking were investigated. Using a targeted RNAi screen strategy, Buenaventura and colleagues identified key modulators of GLP-1R endocytic trafficking and signaling that may provide novel targets to increase insulin secretion in T2D **[12]**. Clathrin, dynamin1, AP2, sorting nexins (SNX) were found to increase while huntingtin-interacting protein 1 (HIP1), HIP14, GASP-1, and Nedd4 were shown to decrease insulin secretion in response to the GLP-1 analog exendin-4. HIP1 couples the cell surface GLP-1R activation with clathrin-dependent endocytosis. SNX proteins control the balance between GLP-1R recycling and lysosomal degradation regulating the β-cell responses to GLP-1 **[12]**. A series of biased GLP-1R agonists with variable propensities for GLP-1R internalization and recycling were tested. Compounds that prompt less GLP-1R internalization and retain the receptor at the plasma membrane were reported to favor greater and long-term glucose-induced insulin secretion. These compounds elicited glycemic benefits in mice **[13]**. Translocation of active GLP-1Rs into liquid-ordered plasma membrane nanodomains were also found to be essential for optimal coordination of clathrin-mediated endocytosis and intracellular signaling. Biased GLP-1R agonists and small molecule allosteric modulators were described to both influence GLP-1R nanodomain internalization and signaling. These molecular processes may be relevant to GLP-1R actions in β-cells and might be therapeutically targetable **[14, 15]**.

Glucagon and somatostatin receptors

The islet hormones glucagon and somatostatin affect β-cell function through paracrine effects within the islets: glucagon released from α-cells stimulates insulin secretion and somatostatin released from δ-cells inhibits insulin secretion. Somatostatin from δ-cells acts on SSTR2 receptor coupled to Gi/Go proteins, which results in the inhibition of adenylate cyclase activity and a decrease in cAMP production. δ-cells and the paracrine interaction between the δ-cells and β-cells were shown to be essential for neonatal survival, normal islet function and glucose homeostasis **[16]**. Glucagon receptors (Gcgr) are also expressed on β-cells, and glucagon stimulates insulin secretion. Binding of glucagon results in the activation of Gαs, adenylate cyclase activity and in an increase in cAMP production. Rodriguez Diaz and colleagues confirmed that glucagon secreted by α-cells plays a major role in regulating the neighboring β-cell through paracrine interactions **[17]**.

Lipid-binding GPCRs

Activation of GPR40 is known to potentiate glucose-induced insulin secretion from β-cells and enhances incretin hormone release from enteroendocrine cells of the small intestine. When activated by long-chain free fatty acids such as palmitate and oleic acid, GPR40 stimulates PLC through Gαq coupling. The IP_3 pathway was found to play an important role in GPR40-mediated potentiation of glucose-induced insulin release in β-cells **[18]**. Full agonist and synthetic small-molecule superagonists of GPR40 enhancing insulin secretion in a glucose-dependent manner *in vitro* and *in vivo* were recently described **[19-21]**. A light-

controllable GPR40 agonist (FAAzo-10) was reported to be a useful tool to investigate the effects of fatty acids-derivatives in mouse β-cell function **[22]**.
Activation of the G-protein coupled receptor 119 (GPR119) expressed in β-cells and intestinal L cells both stimulates insulin secretion and GLP-1 release. Activation of GPR119 in β-cells by lysophosphatidylcholine and oleoylethanolamide increases cAMP and insulin secretion. Investigations in GPR119 drug discovery were conducted, and novel structural diverse small molecules modulators of GPR119 were recently found **[23, 24]**.
Free Fatty Acide Receptor 4 (FFAR4) also called GPR120 is also expressed in β-cells. Activation of GPR120 stimulates Akt/ERK1/2 and PLC/Ca^{2+} signaling pathways and regulates insulin secretion, suggesting GPR120 as a valuable therapeutic target for T2D **[25]**.
The adhesion G-protein coupled receptor 56 (GPR56) is the most abundant islet-expressed GPCR, indicating a potential role in pancreatic islet function. Olaniru and colleagues reported that this GPCR can be activated by its endogenous ligand extracellular matrix collagen III, and when activated increases insulin secretion **[26]**.
The role of free fatty acid receptor 2 (FFAR2)/G-protein coupled receptor 43 in mediating the effects of the short chain fatty acids sodium acetate (SA) and sodium propionate (SP) on islet function was recently investigated. This GPCR was shown to mediate both the stimulatory effects of SA and SP on insulin secretion and their protective effects against apoptosis **[27]**.

Neurotransmitter receptor

Activation of the parasympathetic nerves stimulates insulin secretion. The major parasympathetic neurotransmitters are acetylcholine (Ach), vasoactive intestinal polypeptide (VIP), pituitary, adenylate cyclase activating polypeptide (PACAP) and gastrin releasing peptide (GRP) **[28]**. M_3 muscarinic ACh receptors (M3Rs) are functionally expressed in β-cells and enhance insulin secretion *via* coupling to Gαq activating PLC. A positive allosteric modulator (PAMs) of M3R function was found to improve glucose homeostasis in mice by promoting insulin secretion, suggesting that M3R PAMs may become clinically useful as novel antidiabetic agents **[29]**.

Novel GPCRs expressed in β-cells

GPR55 is a cannabinoid receptor coupled to Gαq signaling. GPR55 activation was shown to increase glucose-induced insulin secretion, to decrease ER stress-mediated apoptosis, to up-regulate anti-apoptotic genes such as Bcl-2 and Bcl-xL, and to induce the phosphorylation/activation of the transcription factor cAMP Response Element Binding protein (CREB) crucial for β-cell survival **[30, 31]**.
A class A of GPCR family, GPR142, has been recently reported to be highly expressed in β-cells, and to play a role for the maintenance of β-cell function and the potentiation of glucose-stimulated insulin secretion **[32-34]**.
The Trace amine-associated receptor 1 (TAAR1) is a GPCR expressed in β-cells. Following activation, TAAR1 was shown to be coupled to Gαs-signaling pathways enhancing

PKA/Epac-dependent insulin secretion, mitogen-activated protein kinase (MAPK), CREB signaling and β-cell proliferation **[35]**.
The olfactory receptor chemo-sensing machinery was reported to be functional in β-cells and to regulate the insulin secretion. Olfactory receptor isoforms were found to be expressed in pancreatic islets and in a β-cell line (i.e. MIN6) including OLFR15 and OLFR821. A medium-chain fatty acid contained in food, octanoic acid, which interacts with OLFR15, potentiates glucose-stimulated insulin secretion, and improves glucose tolerance *in vivo* **[36].**

New technologies to investigate GPCR expression and signaling

A microfluidic system allowing the registration of intracellular signaling dynamics and hormone secretion within the pancreatic islets was developed and confirmed differences in GPCR signaling pathways between human β- and α-cells **[37]**.
Using quantification of mRNAs encoding all peptide ligands of GPCRs in isolated human and mouse pancreatic islets, Atanes and coworkers proposed detailed islet GPCR peptide ligand atlases favoring the identification of GPCR/peptide signaling pathways relevant for human islet physiology **[38]**.
Quantitative markers to investigate and to evaluate the β-cell mass in human pancreas are still lacking. GPR44 was recently proposed as a putative marker for β-cells, and potential target for visualization of β-cell mass. Development of ligands in clinical testing is now needed to further investigate the role of GPR44 as a surrogate marker for β-cell mass in humans **[39]**.

Toward the development of new therapy for T2D: Dual agonist and triagonist strategy to activate GPCRs

Current pharmacological therapies that target single GPCR were reported to exert limited efficacy for T2D treatment. It is important to note that novel approaches with hybrid peptides designed that activate more than one GPCR at once in order to generate beneficial effects through synergistic actions have shown great promising results for T2D treatment. Unimolecular dual and tri-agonists, mainly associated with GPCRs like GLP-1/Glucagon/GIP receptors, have shown great efficacy in preclinical models to preserve insulin secretion. Theses unimolecular dual and tri-agonists are currently being evaluated in clinical trials to study their safety and beneficial effects in humans and T2D patients **[40-45]**.

Signaling crosstalks between GPCRs, tyrosine kinase and sulfonylurea receptors

We and others reported signaling crosstalks between GPCRs and tyrosine kinase receptors controlling β-cell function and survival. Regulation of FFAR4 (GPR120) by activation of receptor tyrosine kinases was recently reported. Insulin, insulin-like growth factor-1, epidermal growth factor, and to a lesser extent, platelet-derived growth factor, were found to induce GPR120 internalization. Whether this new evidenced signaling crosstalk between FFAR4/GPR120 and tyrosine kinase receptors is functional and plays a role in β-cell function remain to be studied **[46]**.

Recently, Hart and colleagues demonstrated that multivalent activation of different type of receptors such as GLP-1R and sulfonylurea receptors modulated β-cell cAMP and calcium second messengers and increased glucose-stimulated insulin secretion in a dose-dependent manner **[42]**. β-Arrestin 1 and β-Arrestin 2 are well described as intracellular scaffold and signaling molecules regulating key functions of GPCRs, such as desensitization and internalization. Recently, Barella and colleagues reported that β-Arrestin 1 enhanced sulfonylurea stimulated insulin secretion by promoting sulfonylurea-mediated activation of Epac2. β-Arrestin 1 was found to directly interact with Epac2. Sulfonylurea such as glibenclamide promoted β-Arrestin 1/Epac2 complex formation, triggering enhanced Rap1 signaling and insulin secretion. Strategies aimed at promoting β-Arrestin 1 signaling in β-cells may prove useful for the development of efficacious antidiabetic drugs targeting not only GPCRs but also sulfonylurea receptor **[47]**.

Conclusion

GPCRs expressed in β-cells receive considerable attention because of their potential as targets in drug development for T2D treatment. Over the next few years, the complex interdependencies between the different messengers and signaling pathways engaged by the activation of GPCRs in β-cells that regulate and shape the insulin secretory response have to be considered. In addition, GPCRs with known ligands need to be further studied in terms of ligand specificity, intracellular signaling, endocytic trafficking and recycling.

Figure Legend

Figure 1. Insulin secretion induced by glucose and modulated by GPCRs. After its entry in β-cells, glucose is metabolized by glycolysis leading to production of pyruvate. Pyruvate enters Krebs cycle in mitochondria increasing ATP/ADP ratio. This favors the closure of ATP-sensitive potassium (KATP) channels, membrane depolarization triggering calcium entry through the opening of voltage-gated calcium channels (VGCC) leading to insulin secretion. G-protein coupled receptors (GPCRs) coupled to Gαq and Gαs proteins act on phospholipase C (PLC) and adenylate cyclase (AC) respectively. Inositol triphosphate (IP_3), diacylglycerol (DAG) stimulate protein kinase C (PKC) while cAMP production activates protein kinase A (PKA) and Epac which potentiate the glucose-induced insulin secretion. Gαi coupling leads the inhibition of AC, reducing cAMP production and decreasing insulin secretion.

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Conflict of interest statement

Nothing declared.

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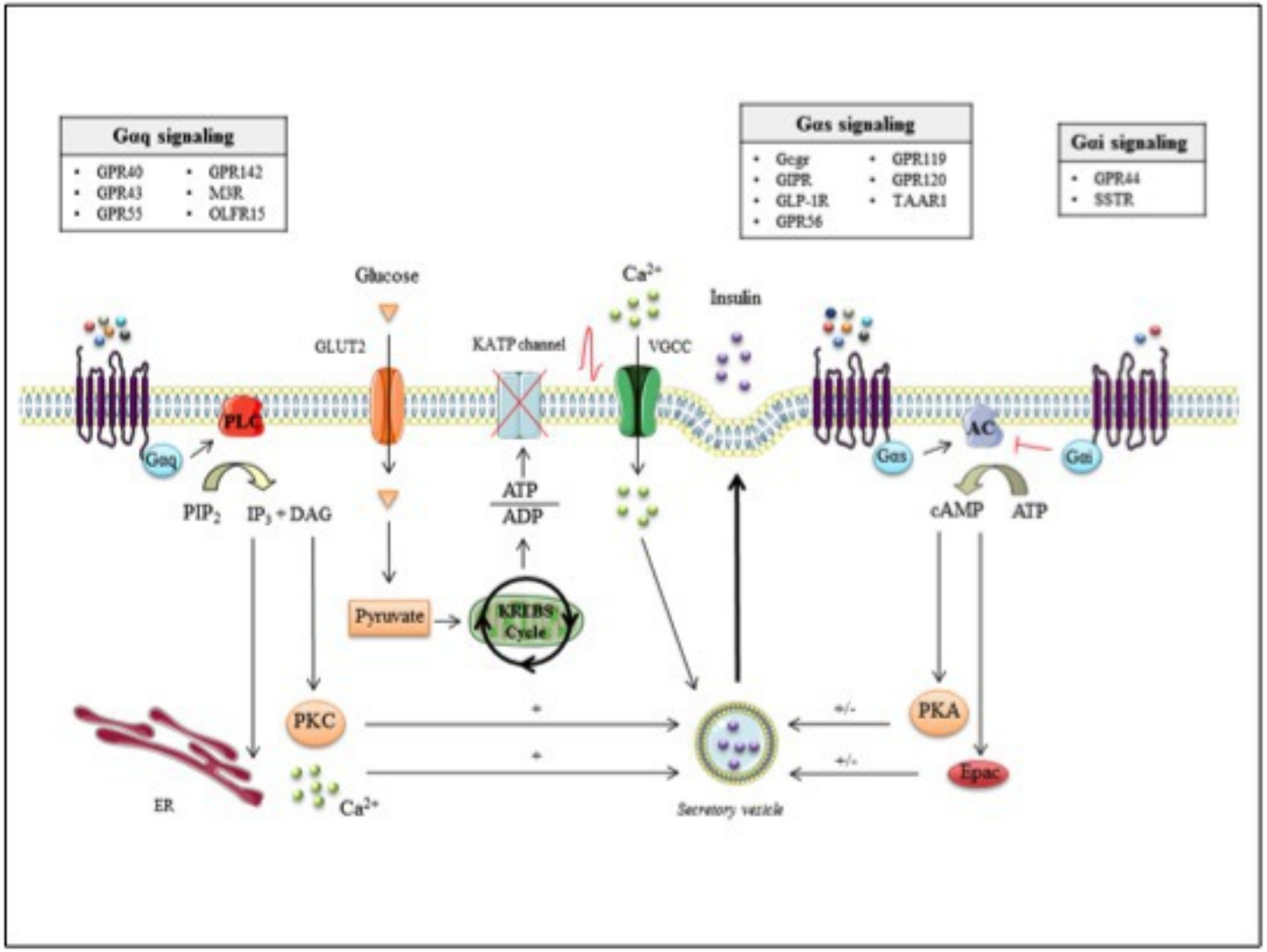

Gαq signaling
GPR40
GPR43
GPR55
GPR142
M3R
OLFR15
Gαs signaling
Gcgr
GIPR
GLP-1R
GPR56
GPR119
GPR120
TAAR1
Gαi signaling
GPR44
SSTR
Glucose
GLUT2
KATP channel
Ca2+
VGCC
Insulin
PLC
Gαq
PIP2
IP3 + DAG
ATP
ADP
Pyruvate
KREBS Cycle
Gαs
AC
Gαi
cAMP
ATP
PKC
PKA
Epac
ER
Ca2+
Secretory vesicle
+
+
+/-
+/-

Table 1

Receptor	Ligand	G protein signaling	Effect on Insulin Secretion
B2	Noradrenaline	Gαs	Stimulation
Gcgr	Glucagon		
GIPR	GIP		
GLP-1R	GLP-1RA		
GPR30	Estogen		
GPR39	Obestatin/Zn^{2+}		
GPR56	Collagen III		
GPR119	Fatty Acid		
GPR120	Fatty Acid		
TGR5	Oleanic Acid		
TAAR1	Trace Amine		
PAC1	PACAP		
P2Y	ATP/ADP		
VPAC2	VIP/PACAP		
A2	Noradrenaline	Gαi	Inhibition
CB1R	Cannabinoids		
GHS-R	Ghrelin		
GPR44	Prostaglandin D_2		
NPYR	Peptide YY		
SSTR2	Somatostatin		
Y1	Neuropeptide Y		
AT1	Angiotensin II	Gαq	Stimulation
CCK1	CCK		
FZD	Carbamazepine		
GPR39	Obestatin/Zn^{2+}		
GPR40	Fatty Acid		
GPR43	Fatty Acid		
GPR54	Kisspeptin		
GPR55	Cannabinoids		
GPR142	Rhodopsin		
IL-6R	IL-6		
M3R	Acetylcholine		
OLFR15	Octanoic Acid		
HTR2B	Serotonin		
V1B	Vasopressin		