



**HAL**  
open science

# G-protein–coupled receptors controlling pancreatic $\beta$ -cell functional mass for the treatment of type 2 diabetes

Morgane Delobel, Stéphane Dalle

## ► To cite this version:

Morgane Delobel, Stéphane Dalle. G-protein–coupled receptors controlling pancreatic  $\beta$ -cell functional mass for the treatment of type 2 diabetes. *Current Opinion in Endocrine and Metabolic Research*, 2021, 16, pp.113 - 118. 10.1016/j.coemr.2020.09.010 . hal-03493171

**HAL Id: hal-03493171**

**<https://hal.science/hal-03493171>**

Submitted on 15 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# **G-protein coupled receptors controlling pancreatic $\beta$ -cell functional mass for the treatment of Type 2 Diabetes**

Morgane Delobel<sup>1</sup>, Stéphane Dalle<sup>1</sup>

## **Addresses**

<sup>1</sup> Institut de Génomique Fonctionnelle, CNRS, INSERM, Université Montpellier, Montpellier  
France

Corresponding author: Dalle, Stéphane

([stephane.dalle@igf.cnrs.fr](mailto:stephane.dalle@igf.cnrs.fr))

Institut de Génomique Fonctionnelle, 141 rue de la Cardonille, 34094 Montpellier cedex 05,  
France

## ***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  $\beta$ -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  $\beta$ -cells. This review summarizes knowledge over the last two years on GPCRs functionally expressed in  $\beta$ -cells, which present key features for the development of therapy for type 2 diabetes.

## ***Keywords***

G-protein coupled receptor, Pancreatic  $\beta$ -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  $\beta$ -cell function. The insulin resistance of T2D, although important for its pathophysiology, is not sufficient to establish the disease unless major deficiency of  $\beta$ -cell function co-exists [2]. Reduced  $\beta$ -cell mass has also been proposed to be associated with T2D [3]. Therefore, innovative therapeutic strategies aiming at preserving  $\beta$ -cell function and survival are of great interest to slow the progression or even to prevent T2D [4, 5].  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -cell signaling, involving the cAMP/protein kinase A (PKA)/Epac, and the inositol triphosphate (IP<sub>3</sub>)/diacylglycerol (DAG) pathways, as well as changes in protein phosphorylation and protein acylation. The cAMP/PKA and the IP<sub>3</sub>/DAG pathways engaged during the activation of GPCRs are among the most important signaling pathways for the  $\beta$ -cell biology (Figure 1). G $\alpha$ s mediates increases in intracellular cAMP associated with increased insulin secretion, while G $\alpha$ i mediates decreases in intracellular cAMP and inhibition of insulin secretion. G $\alpha$ q mediates increases in IP<sub>3</sub> and DAG production through the activation of phospholipase C (PLC) associated with increased release of calcium (Ca<sup>2+</sup>) 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  $\beta$ -cell survival programs [9]. Table 1 presents the GPCRs expressed in  $\beta$ -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 G $\alpha$ s with subsequent activation of adenylate cyclase and elevation of cAMP levels in  $\beta$ -cells. When activated, GLP-1R potentiates glucose-induced insulin secretion through cAMP production. GLP-1R is a key target for T2D treatment [11].

Beyond  $G\alpha_s$  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  $\beta$ -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  $\beta$ -cells and might be therapeutically targetable [14, 15].

### ***Glucagon and somatostatin receptors***

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

### ***Lipid-binding GPCRs***

Activation of GPR40 is known to potentiate glucose-induced insulin secretion from  $\beta$ -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  $G\alpha_q$  coupling. The  $IP_3$  pathway was found to play an important role in GPR40-mediated potentiation of glucose-induced insulin release in  $\beta$ -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  $\beta$ -cell function [22].

Activation of the G-protein coupled receptor 119 (GPR119) expressed in  $\beta$ -cells and intestinal L cells both stimulates insulin secretion and GLP-1 release. Activation of GPR119 in  $\beta$ -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  $\beta$ -cells. Activation of GPR120 stimulates Akt/ERK1/2 and PLC/Ca<sup>2+</sup> 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<sub>3</sub> muscarinic ACh receptors (M3Rs) are functionally expressed in  $\beta$ -cells and enhance insulin secretion *via* coupling to G $\alpha_q$  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 $\beta$ -cells*

GPR55 is a cannabinoid receptor coupled to G $\alpha_q$  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  $\beta$ -cell survival [30, 31].

A class A of GPCR family, GPR142, has been recently reported to be highly expressed in  $\beta$ -cells, and to play a role for the maintenance of  $\beta$ -cell function and the potentiation of glucose-stimulated insulin secretion [32-34].

The Trace amine-associated receptor 1 (TAAR1) is a GPCR expressed in  $\beta$ -cells. Following activation, TAAR1 was shown to be coupled to G $\alpha_s$ -signaling pathways enhancing

PKA/Epac-dependent insulin secretion, mitogen-activated protein kinase (MAPK), CREB signaling and  $\beta$ -cell proliferation [35].

The olfactory receptor chemo-sensing machinery was reported to be functional in  $\beta$ -cells and to regulate the insulin secretion. Olfactory receptor isoforms were found to be expressed in pancreatic islets and in a  $\beta$ -cell line (i.e. MIN6) including OLF15 and OLF821. A medium-chain fatty acid contained in food, octanoic acid, which interacts with OLF15, 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  $\beta$ - and  $\alpha$ -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  $\beta$ -cell mass in human pancreas are still lacking. GPR44 was recently proposed as a putative marker for  $\beta$ -cells, and potential target for visualization of  $\beta$ -cell mass. Development of ligands in clinical testing is now needed to further investigate the role of GPR44 as a surrogate marker for  $\beta$ -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. These 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  $\beta$ -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  $\beta$ -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  $\beta$ -cell cAMP and calcium second messengers and increased glucose-stimulated insulin secretion in a dose-dependent manner [42].  $\beta$ -Arrestin 1 and  $\beta$ -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  $\beta$ -Arrestin 1 enhanced sulfonylurea stimulated insulin secretion by promoting sulfonylurea-mediated activation of Epac2.  $\beta$ -Arrestin 1 was found to directly interact with Epac2. Sulfonylurea such as glibenclamide promoted  $\beta$ -Arrestin 1/Epac2 complex formation, triggering enhanced Rap1 signaling and insulin secretion. Strategies aimed at promoting  $\beta$ -Arrestin 1 signaling in  $\beta$ -cells may prove useful for the development of efficacious antidiabetic drugs targeting not only GPCRs but also sulfonylurea receptor [47].

### ***Conclusion***

GPCRs expressed in  $\beta$ -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  $\beta$ -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  $\beta$ -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  $G_{\alpha q}$  and  $G_{\alpha s}$  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.  $G_{\alpha i}$  coupling leads the inhibition of AC, reducing cAMP production and decreasing insulin secretion.

### ***Acknowledgements***

Morgane Delobel is supported by CIFRE grant Phd fellowship from MedBioMed.

### ***Conflict of interest statement***

Nothing declared.

## **References**

Papers of particular interest, published within the period of review, have been highlighted as:

\* of special interest

[1] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, Committee IDFDA. **Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition.** *Diabetes Res Clin Pract* 2019; 157:107843.

[2] Nolan CJ, Prentki M. **Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift.** *Diab Vasc Dis Res* 2019; 16:118-127.

[3] Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. **Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes.** *Diabetes* 2003; 52:102-110.

[4] Kahn SE, Cooper ME, Del Prato S. **Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future.** *Lancet* 2014; 383:1068-1083.

[5] Yehya A, Sadhu AR. **New Therapeutic Strategies for Type 2 Diabetes (CME).** *Methodist Debakey Cardiovasc J* 2018; 14:281-288.

[6] Burgos-Moron E, Abad-Jimenez Z, Maranon AM, Iannantuoni F, Escribano-Lopez I, Lopez-Domenech S, Salom C, Jover A, Mora V, Roldan I, Sola E, Rocha M, Victor VM. **Relationship Between Oxidative Stress, ER Stress, and Inflammation in Type 2 Diabetes: The Battle Continues.** *J Clin Med* 2019; 8.

[7] Moulle VS, Ghislain J, Poitout V. **Nutrient regulation of pancreatic beta-cell proliferation.** *Biochimie* 2017; 143:10-17.

[8] Henquin JC. **Triggering and amplifying pathways of regulation of insulin secretion by glucose.** *Diabetes* 2000; 49:1751-1760.

[9] Winzell MS, Ahren B. **G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes.** *Pharmacol Ther* 2007; 116:437-448.

[10] Persaud SJ. **Islet G-protein coupled receptors: therapeutic potential for diabetes.** *Curr Opin Pharmacol* 2017; 37:24-28.

[11] Baggio LL, Drucker DJ. **Biology of incretins: GLP-1 and GIP.** *Gastroenterology* 2007; 132:2131-2157.

[12] Buenaventura T, Kanda N, Douzenis PC, Jones B, Bloom SR, Chabosseau P, Correa IR, Jr., Bosco D, Piemonti L, Marchetti P, Johnson PR, Shapiro AMJ, Rutter GA, Tomas A. **A**

**Targeted RNAi Screen Identifies Endocytic Trafficking Factors That Control GLP-1 Receptor Signaling in Pancreatic beta-Cells.** Diabetes 2018; 67:385-399.

[13] Jones B, Buenaventura T, Kanda N, Chabosseau P, Owen BM, Scott R, Goldin R, Angkathunyakul N, Correa IR, Jr., Bosco D, Johnson PR, Piemonti L, Marchetti P, Shapiro AMJ, Cochran BJ, Hanyaloglu AC, Inoue A, Tan T, Rutter GA, Tomas A, Bloom SR. **Targeting GLP-1 receptor trafficking to improve agonist efficacy.** Nat Commun 2018; 9:1602.

[14] Buenaventura T, Bitsi S, Laughlin WE, Burgoyne T, Lyu Z, Oqua AI, Norman H, McGlone ER, Klymchenko AS, Correa IR, Jr., Walker A, Inoue A, Hanyaloglu A, Grimes J, Koszegi Z, Calebiro D, Rutter GA, Bloom SR, Jones B, Tomas A. **Agonist-induced membrane nanodomain clustering drives GLP-1 receptor responses in pancreatic beta cells.** PLoS Biol 2019; 17:e3000097.

\* **This study shows that organization of GLP-1R into plasma membrane lipid nanodomains is important for optimal intracellular signaling. Biased agonists regulate these nanodomain and downstream signaling.**

[15] Manchanda Y, Bitsi S, Kang Y, Jones B, Tomas A. **Spatiotemporal Control of GLP-1 Receptor Activity.** Current Opinion in Endocrine and Metabolic Research 2020.

[16] Li N, Yang Z, Li Q, Yu Z, Chen X, Li JC, Li B, Ning SL, Cui M, Sun JP, Yu X. **Ablation of somatostatin cells leads to impaired pancreatic islet function and neonatal death in rodents.** Cell Death Dis 2018; 9:682.

[17] Rodriguez-Diaz R, Molano RD, Weitz JR, Abdulreda MH, Berman DM, Leibiger B, Leibiger IB, Kenyon NS, Ricordi C, Pileggi A, Caicedo A, Berggren PO. **Paracrine Interactions within the Pancreatic Islet Determine the Glycemic Set Point.** Cell Metab 2018; 27:549-558 e544.

\* **This study shows paracrine effects of  $\alpha$ -cells and  $\beta$ -cells which determine the glycemic regulation within the organism.**

[18] Usui R, Yabe D, Fauzi M, Goto H, Botagarova A, Tokumoto S, Tatsuoka H, Tahara Y, Kobayashi S, Manabe T, Baba Y, Kurosaki T, Herrera PL, Ogura M, Nagashima K, Inagaki N. **GPR40 activation initiates store-operated Ca(2+) entry and potentiates insulin secretion via the IP3R1/STIM1/Orai1 pathway in pancreatic beta-cells.** Sci Rep 2019; 9:15562.

[19] Huang H, Meegalla SK, Lanter JC, Winters MP, Zhao S, Littrell J, Qi J, Rady B, Lee PS, Liu J, Martin T, Lam WW, Xu F, Lim HK, Wilde T, Silva J, Otieno M, Pocai A, Player MR. **Discovery of a GPR40 Superagonist: The Impact of Aryl Propionic Acid alpha-Fluorination.** ACS Med Chem Lett 2019; 10:16-21.

[20] Abdel-Magid AF. **GPR40 Receptor Agonists for the Treatment of Type 2 Diabetes and Related Diseases.** ACS Med Chem Lett 2018; 9:870-871.

[21] Meegalla SK, Huang H, Martin T, Xu J, Zhao S, Liu J, Hall M, Gunnet J, Wang Y, Rady B, Silva J, Otieno M, Arnoult E, Paul Lee S, Poci A, Player MR. **Discovery of a novel potent GPR40 full agonist.** *Bioorg Med Chem Lett* 2018; 28:720-726.

[22] Frank JA, Yushchenko DA, Fine NHF, Duca M, Citir M, Broichhagen J, Hodson DJ, Schultz C, Trauner D. **Optical control of GPR40 signalling in pancreatic beta-cells.** *Chem Sci* 2017; 8:7604-7610.

[23] Nieto A, Fernandez-Vega V, Spicer TP, Sturchler E, Adhikari P, Kennedy N, Mandat S, Chase P, Scampavia L, Bannister T, Hodder P, McDonald PH. **Identification of Novel, Structurally Diverse, Small Molecule Modulators of GPR119.** *Assay Drug Dev Technol* 2018; 16:278-288.

[24] Matsumoto K, Yoshitomi T, Ishimoto Y, Tanaka N, Takahashi K, Watanabe A, Chiba K. **DS-8500a, an Orally Available G Protein-Coupled Receptor 119 Agonist, Upregulates Glucagon-Like Peptide-1 and Enhances Glucose-Dependent Insulin Secretion and Improves Glucose Homeostasis in Type 2 Diabetic Rats.** *J Pharmacol Exp Ther* 2018; 367:509-517.

[25] Wang Y, Xie T, Zhang D, Leung PS. **GPR120 protects lipotoxicity-induced pancreatic beta-cell dysfunction through regulation of PDX1 expression and inhibition of islet inflammation.** *Clin Sci (Lond)* 2019; 133:101-116.

[26] Olaniru OE, Pingitore A, Giera S, Piao X, Castanera Gonzalez R, Jones PM, Persaud SJ. **The adhesion receptor GPR56 is activated by extracellular matrix collagen III to improve beta-cell function.** *Cell Mol Life Sci* 2018; 75:4007-4019.

[27] Pingitore A, Gonzalez-Abuin N, Ruz-Maldonado I, Huang GC, Frost G, Persaud SJ. **Short chain fatty acids stimulate insulin secretion and reduce apoptosis in mouse and human islets in vitro: Role of free fatty acid receptor 2.** *Diabetes Obes Metab* 2019; 21:330-339.

[28] Gylfe E, Tengholm A. **Neurotransmitter control of islet hormone pulsatility.** *Diabetes Obes Metab* 2014; 16 Suppl 1:102-110.

[29] Zhu L, Rossi M, Cohen A, Pham J, Zheng H, Dattaroy D, Mukaibo T, Melvin JE, Langel JL, Hattar S, Matschinsky FM, Appella DH, Doliba NM, Wess J. **Allosteric modulation of beta-cell M3 muscarinic acetylcholine receptors greatly improves glucose homeostasis in lean and obese mice.** *Proc Natl Acad Sci U S A* 2019; 116:18684-18690.

\* **This study shows efficacy of an allosteric agent acting on M3R to improve plasma insulin and glucose tolerance without side effects.**

[30] McCloskey AG, Miskelly MG, Moore CBT, Nesbit MA, Christie KA, Owolabi AI, Flatt PR, McKillop AM. **CRISPR/Cas9 gene editing demonstrates metabolic importance of GPR55 in the modulation of GIP release and pancreatic beta cell function.** *Peptides* 2020; 125:170251.

[31] Vong CT, Tseng HHL, Kwan YW, Lee SM, Hoi MPM. **Novel protective effect of O-1602 and abnormal cannabidiol, GPR55 agonists, on ER stress-induced apoptosis in pancreatic beta-cells.** Biomed Pharmacother 2019; 111:1176-1186.

[32] Al-Amily IM, Duner P, Groop L, Salehi A. **The functional impact of G protein-coupled receptor 142 (Gpr142) on pancreatic beta-cell in rodent.** Pflugers Arch 2019; 471:633-645.

[33] Kaushik AC, Kumar S, Wei DQ, Sahi S. **Structure Based Virtual Screening Studies to Identify Novel Potential Compounds for GPR142 and Their Relative Dynamic Analysis for Study of Type 2 Diabetes.** Front Chem 2018; 6:23.

[34] Rudenko O, Shang J, Munk A, Ekberg JP, Petersen N, Engelstoft MS, Egerod KL, Hjorth SA, Wu M, Feng Y, Zhou YP, Mokrosinski J, Thams P, Reimann F, Gribble F, Rehfeld JF, Holst JJ, Treebak JT, Howard AD, Schwartz TW. **The aromatic amino acid sensor GPR142 controls metabolism through balanced regulation of pancreatic and gut hormones.** Mol Metab 2019; 19:49-64.

[35] Michael ES, Covic L, Kuliopulos A. **Trace amine-associated receptor 1 (TAAR1) promotes anti-diabetic signaling in insulin-secreting cells.** J Biol Chem 2019; 294:4401-4411.

[36] Munakata Y, Yamada T, Imai J, Takahashi K, Tsukita S, Shirai Y, Kodama S, Asai Y, Sugisawa T, Chiba Y, Kaneko K, Uno K, Sawada S, Hatakeyama H, Kanzaki M, Miyazaki JI, Oka Y, Katagiri H. **Olfactory receptors are expressed in pancreatic beta-cells and promote glucose-stimulated insulin secretion.** Sci Rep 2018; 8:1499.

[37] Walker JT, Haliyur R, Nelson HA, Ishahak M, Poffenberger G, Aramandla R, Reihsmann C, Luchsinger JR, Saunders DC, Wang P, Garcia-Ocana A, Bottino R, Agarwal A, Powers AC, Brissova M. **Integrated human pseudoislet system and microfluidic platform demonstrate differences in GPCR signaling in islet cells.** JCI Insight 2020; 5.

\* **This study shows the differences in GPCR signaling pathways between  $\alpha$ -cells and  $\beta$ -cells thanks to the use of pseudoislets and microfluidic system.**

[38] Atanes P, Ruz-Maldonado I, Hawkes R, Liu B, Zhao M, Huang GC, Al-Amily IM, Salehi A, Amisten S, Persaud SJ. **Defining G protein-coupled receptor peptide ligand expressomes and signalomes in human and mouse islets.** Cell Mol Life Sci 2018; 75:3039-3050.

[39] Eriksson O. **GPR44 as a Target for Imaging Pancreatic Beta-Cell Mass.** Curr Diab Rep 2019; 19:49.

[40] Pathak NM, Pathak V, Gault VA, McClean S, Irwin N, Flatt PR. **Novel dual incretin agonist peptide with antidiabetic and neuroprotective potential.** Biochem Pharmacol 2018; 155:264-274.

[41] Chepurny OG, Bonaccorso RL, Leech CA, Wollert T, Langford GM, Schwede F, Roth CL, Doyle RP, Holz GG. **Chimeric peptide EP45 as a dual agonist at GLP-1 and NPY2R receptors.** Sci Rep 2018; 8:3749.

[42] Hart NJ, Weber C, Papas KK, Limesand SW, Vagner J, Lynch RM. **Multivalent activation of GLP-1 and sulfonylurea receptors modulates beta-cell second-messenger signaling and insulin secretion.** Am J Physiol Cell Physiol 2019; 316:C48-C56.

[43] Tillner J, Posch MG, Wagner F, Teichert L, Hijazi Y, Einig C, Keil S, Haack T, Wagner M, Bossart M, Larsen PJ. **A novel dual glucagon-like peptide and glucagon receptor agonist SAR425899: Results of randomized, placebo-controlled first-in-human and first-in-patient trials.** Diabetes Obes Metab 2019; 21:120-128.

[44] Ambery P, Parker VE, Stumvoll M, Posch MG, Heise T, Plum-Moerschel L, Tsai LF, Robertson D, Jain M, Petrone M, Rondinone C, Hirshberg B, Jermutus L. **MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study.** Lancet 2018; 391:2607-2618.

\* **This study (in a phase 2a) shows an improvement of glycemia and bodyweight in obese individuals with T2D after the use of MEDI0382, a dual agonist of GLP-1R and glucagon receptor.**

[45] Capozzi ME, DiMarchi RD, Tschop MH, Finan B, Campbell JE. **Targeting the Incretin/Glucagon System With Triagonists to Treat Diabetes.** Endocr Rev 2018; 39:719-738.

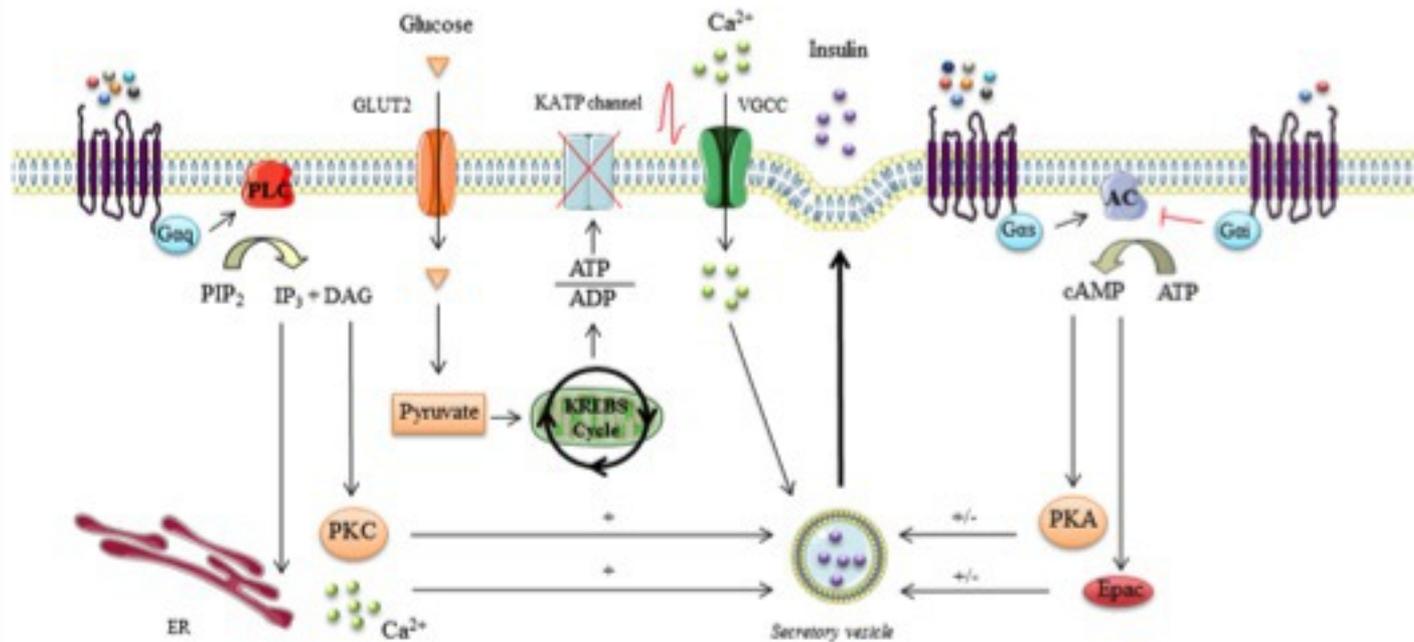
[46] Villegas-Comonfort S, Guzman-Silva A, Romero-Avila MT, Takei Y, Tsujimoto G, Hirasawa A, Garcia-Sainz JA. **Receptor tyrosine kinase activation induces free fatty acid 4 receptor phosphorylation, beta-arrestin interaction, and internalization.** Eur J Pharmacol 2019; 855:267-275.

[47] Barella LF, Rossi M, Zhu L, Cui Y, Mei FC, Cheng X, Chen W, Gurevich VV, Wess J. **beta-Cell-intrinsic beta-arrestin 1 signaling enhances sulfonylurea-induced insulin secretion.** J Clin Invest 2019; 129:3732-3737.

G $\alpha_q$ signaling	
• GPR40	• GPR142
• GPR43	• M3R
• GPR55	• OLFRL15

G $\alpha_s$ signaling	
• Gcgr	• GPR119
• GIPR	• GPR120
• GLP-1R	• TAAR1
• GPR56	

G $\alpha_i$ signaling	
• GPR44	
• SSTR	



**Table 1**

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