G-protein-coupled receptors and islet function -

Implications for treatment of type 2 diabetes

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Abstract

Islet function is regulated by a number of different signals. A main signal is generated by glucose, which stimulates insulin secretion and inhibits glucagon secretion. The glucose effects are modulated by many factors, including hormones, neurotransmitters and nutrients. Several of these factors signal through guanine nucleotide-binding protein (G-protein) coupled receptors (GPCRs). Examples of islet GPCRs are GPR40 and GPR119, which are GPCRs with fatty acids as ligands, the receptors for the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), the receptors for the islet hormones glucagon and somatostatin, the receptors for the classical neurotransmittors acetylcholine (M_3 muscarinic receptors) and noradrenaline (β_2- and α_2-adrenoceptors) and for the neuropeptides pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal polypeptide (VIP) (PAC_1 and $VPAC_2$ receptors), cholecystokinin (CCK_A receptors) and neuropeptide Y (NPY Y1 receptors). Other islet GPCRs are the cannabinoid receptor (CB_1 receptors), the vasopressin receptors ($V1_B$ receptors) and the purinergic receptors (P_{2Y} receptors). The islet GPCRs couple mainly to adenylate cyclase and to phospholipase C (PLC). Since important pharmacological strategies for treatment of type 2 diabetes are stimulation of insulin secretion and inhibition of glucagon secretion, islet GPCRs are potential drug targets. This review summarizes knowledge on islet GPCRs.

Keywords: Islet, insulin secretion, glucagon secretion, GPCR, type 2 diabetes

Abbreviations

ACh, acetylcholine

cAMP, cyclic AMP

CB, cannabinoid

CCK, cholecystokinin

CGRP, calcitonin gene-related peptide

DAG, diacylglycerol

FFA, free fatty acids

G-protein, guanine nucleotide-binding protein

Gcgr, glucagon receptor

GIP, glucose-dependent insulinotropic polypeptide

GLP-1, glucagon-like peptide

GLUT2, glucose transporter 2

GPCR , G-protein-coupled receptor

IP_3, inositol 1,4,5-trisphosphate

NPY, neuropeptide Y

PACAP, pituitary adenylate cyclase activating polypeptide

PI3K, phosphatidylinositol 3-kinase

PKA, protein kinase A

PKC, protein kinase C

PLC, phospholipase C

VIP, vasoactive intestinal polypeptide

Contents

1. Introduction

This review summarizes knowledge on G-protein coupled receptors (GPCR), which are expressed in the pancreatic islets and their potential involvement in islet function, which may have implications for development of novel therapy for type 2 diabetes. In general, GPCRs function to transmit information from extracellular stimuli to intracellular signals. Many GPCRs exist. In fact, the GPCR superfamily is the largest class of cell surface receptors and almost 1,000 GPCRs are thought to be encoded by the human genome (Fredriksson & Schioth, 2005; Perez, 2003, Takeda et al., 2002; Vassilatis et al., 2003). These receptors have diverse roles in that they regulate overall organism homeostasis as well as embryo development, and they are also involved in learning, memory, vision, smell and taste. Some of the GPCRs are thought to be involved in energy homeostasis and in the regulation of islet function. The GPCRs have a wide variety of ligands, spanning from photons, ions, small molecules such as amines, fatty acids, and amino acids, to peptides, proteins, and steroids. Today, approximately 50% of drug targets in the pharmaceutical industry are GPCRs (Klabunde & Hessler, 2002). There are also numerous (>100) orphan GPCRs whose ligands and effects are not yet known (Civelli, 2005). It is also known that many diseases are linked to GPCRs.

2. Structure and signaling pathways of GPCRs

The GPCRs have a similar topology consisting of a core of seven transmembrane-spanning α-helices with three hydrophilic intracellular and three hydrophilic extracellular loops; the N-terminus is located extracellularly and the C-terminus is located intracellularly. Fig. 1 shows a schematic illustration of a GPCR and its coupling to G proteins. The GPCRs are synthesized, folded and assembled in the endoplasmic reticulum. Newly synthesized receptors are packed in vesicles, which transport the receptors to the plasma membranes. During the transportation, they undergo posttranslational modifications (Dong et al. 2007). Upon binding of a ligand to its specific GPCR, it undergoes a conformational change, which is transmitted to the cytoplasmic portion of the protein (Yeagle & Albert, 2007). This enables coupling with an intracellular heterotrimer G protein (GTP binding protein) (Neves et al., 2002). G-proteins consist of three subunits, α, β and γ. A large number of G-proteins have been identified, including G_s, G_i, and G_q. These intracellular G proteins signal by activating or inhibiting enzyme activities. Thus, the G_s effector activates adenylate cyclase, resulting in increased cAMP production, with subsequent activation of protein kinase A (PKA) and the Epac family of cAMP-regulated guanine nucleotide exchange factor, both of which have multiple downstream effectors. G_i has the ability to inhibit adenylate cyclase via $G_{\alpha i}$, but it also signals via $G_{\beta\gamma}$, which couples to phospholipase C-β (PLC-β), K^+ channels, adenylate cyclase and phosphatidylinositol 3-kinase (PI3K). The G_q pathway stimulates PLC-β to produce inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 triggers the release of Ca^{2+} from the endoplasmic reticulum whereas DAG activates protein kinase C (PKC). Finally, following GPCR stimulation, the receptors undergo internalization and are sorted in the endosome for recycling or further transportation to lysosomes for degradation (von Zastrow 2003). However, in spite of a large body of growing knowledge regarding structure, signaling

and trafficking of GPCRs, much remains to be known on these molecular mechanisms (Dong et al. 2007; Yeagle & Albert, 2007).

3. GPCRs expressed in islets

The pancreatic islets consist of several different cell types including α, β, δ and pancreatic polypeptide (PP) cells. The islets are, furthermore, richly vascularized and richly innervated. A most important function of the pancreatic islets is to secrete insulin. Several pathways signal the exocytosis of insulin (Henquin 2004). Glucose acts as the triggering molecule when it is taken up into the cell through the glucose transporter 2 (GLUT2). When glucose is metabolized, it raises the intracellular energy levels by increasing the ATP/ADP ratio. This results in closure of ATP-sensitive K^+ channels and membrane depolarization, which opens the voltage-gated Ca^{2+} channels to increase the influx of Ca^{2+}. Elevation of intracellular Ca^{2+} elicits insulin secretion. These effects of glucose are modulated by several factors to optimize insulin secretion, and several of these factors work through GPCRs. Table 1 lists the receptors covered in this review. Although much remains to be studied regarding molecular mechanisms of islet GPCRs, most studies have been concentrated on β cell function. These studies have shown that activation of islet GPCRs results in different β cell signaling, involving alteration in intracellular levels of cAMP, IP_3 and Ca^{2+}, as well as changes in protein phosphorylation and protein acylation. Fig. 2 illustrates schematically β cell GPCRs and their signaling. The G-proteins are mediators of these intracellular signal transduction pathways (Neves et al., 2002). G_s mediates increases in intracellular cAMP associated with increased insulin secretion, while G_i mediates decreases in intracellular cAMP and inhibition of insulin secretion. G-proteins also regulate ion channels, phospholipases, and distal sites in exocytosis (Kowluru, 2003). Much less is known about the regulation of glucagon secretion but similar pathways which are active in β cells operate also in α cells (Gromada et al., 2007).

4. GPCR as a drug target in the treatment of type 2 diabetes

A normal islet function is a prerequisite for a normal glucose homeostasis. In fact, islet dysfunction is a key event underlying development of type 2 diabetes, as manifested by impaired insulin secretion and increased secretion of glucagon (Dunning et al., 2005; Wajchenberg 2007). Recently, it has also been proposed that reduced β cell mass is associated with type 2 diabetes (Butler et al., 2003; Wajchenberg 2007). Since glycemic control of type 2 diabetes often deteriorates in spite of aggressive treatment (Turner 1998), there is today an active search for novel therapy. A requirement of these therapies is that they target the key pathogenic factors underlying the disease, the islet dysfunction. An important strategy for treatment of diabetes is to stimulate insulin secretion and it is also important to reduce glucagon secretion. Since GPCRs are involved in the regulation of insulin and glucagon secretion, they serve as potential drug targets. Several approaches have been undertaken to target GPCRs for new treatment (Garrido et al., 2006; McKeown et al., 2007).

5. Lipid-binding GPCRs

Besides their function as sources of energy, as building blocks in membrane structures and lipophilic molecules, FFAs are signaling molecules (Nunez, 1997). As such, FFAs have been shown to stimulate both insulin secretion (Haber et al., 2006) and glucagon secretion (Bollheimer et al., 2004, Olofsson et al., 2004). The stimulation by FFAs of insulin secretion was previously thought to be mainly executed through an intracellular effect of the fatty acid species (Corkey et al., 2000). However, FFAs have also been shown to activate islet GPCRs to regulate islet function. An insulinotropic action of FFAs through GPCR was first proposed for GPR40, the activation of which stimulates insulin secretion. (Briscoe et al., 2003; Itoh et al., 2003; Kotarsky et al., 2003). Also GPR41 and GPR43 are fatty-acid-binding GPCRs and

might contribute (Brown et al., 2005; Covington et al., 2006). GPR40 has long-chain FFAs (>C12) as activating ligands (Itoh et al., 2003; Kotarsky et al., 2003), while GPR41 and 43 are activated by short-chain FFAs (<C6) (Brown et al., 2003). Recently, also GRP119 was identified in islets where it might be involved in the FFA-induced insulin secretion (Chu et al., 2007).

5.1 GPR40

GPR40 is highly expressed in mouse, rat and human pancreatic β cells, and thought to be involved in the regulation of FFA-potentiated glucose-stimulated insulin secretion (Itoh et al., 2003; Salehi et al., 2005; Tomita et al., 2006). In fact, GPR40 has been suggested to mediate the majority of the effects of fatty acids on β cells (Itoh et al., 2003; Salehi et al., 2005). GPR40 is coupled to $G_{\alpha q}$ with a subsequent increase in cytosolic Ca^{2+} concentration (Itoh et al., 2003), although also a mechanism through activation of PLC has been proposed (Feng et al., 2006; Fujiwara et al., 2005; Shapiro et al., 2005). The possible role of GPR40 in insulin secretion has been studied using GPR40-deficient mice (GPR40-/-). These mice have impaired acute insulin secretory response to FFAs, which enforces the importance of GRP40 in this respect (Steneberg et al., 2005).

Previous studies have also shown that long-term exposure of islets to FFAs results in impaired glucose-stimulated insulin secretion through a lipotoxic action (Boden, 1999; Haber et al., 2006; Zraika et al., 2002). This effect might be of importance for the long-term deterioration of β cell function in type 2 diabetes. The mechanism of the lipotoxic effects of FFAs in β cells has been shown to be complex and to involve both metabolic and genetic perturbations (Haber et al. 2006). Interestingly, the GPR40-/- mice were protected against the lipotoxic effects on glucose homeostasis caused by high-fat-diet (Steneberg et al. 2005). This suggests

that also this effect by FFAs, besides the stimulation of insulin secretion, may be mediated by GPR40. This conclusion is corroborated by results in transgenic mice with β-cell-specific overexpression of GPR40 (Steneberg et al., 2005). These mice developed overt diabetes due to severely impaired insulin secretion, which is seen in association with perturbed expression of β-cell genes in analogy with changes seen during lipotoxicity. Therefore, GPR40 is important for both FFA-induced potentiation of glucose-stimulated insulin secretion and the deleterious effects of fatty acids.

Besides insulin secretion, FFAs also stimulate glucagon secretion, as demonstrated in isolated rat and mouse islets (Bollheimer et al., 2004, Olofsson et al., 2004). It remains to be established whether GPR40 mediates this effect. A recent study opened up for this possibility, however, since it was demonstrated that GRP40 receptors are identified in glucagon-producing clonal α cells and in mouse α cells (Flodgren et al., 2007).

Recently, efforts have been made to produce small molecule GPR40 receptor agonists and antagonists to investigate their potential as drugs for type 2 diabetes (Briscoe et al., 2006). In clonal β cells, insulin secretion could be potentiated by addition of a GPR40 agonist, suggesting that acute activation of GPR40 may be useful to stimulate insulin secretion (Briscoe et al., 2006). However, since the mouse model with transgenic overexpression of GPR40 exhibited impaired β cell function and type 2 diabetes (Steneberg et al., 2005), chronic activation of the receptor may cause deleterious effects. Therefore, a GPR40 antagonist may be a more efficient concept because patients with type 2 diabetes usually have elevated circulating FFAs. Further studies are needed to evaluate whether GPR40 agonists or antagonists are suitable for antidiabetic treatment.

5.2 GPR41 and GPR43

Two other fatty-acid-binding GPCRs, GPR41 and GPR43, are closely related to GPR40 (Brown et al., 2003). However, in contrast to GPR40, both GPR41 and GPR43 have short fatty acids (C2-C6) as their ligands. GPR41 couples to G_i/G_o proteins, whereas GPR43 mainly couples to G_q-proteins. These receptors are expressed in a variety of tissues, such as in adipose tissue (Brown et al., 2003). In a recent patent applications, both these receptors were reported to be expressed in islets (Leonard et al., 2006; Leonard & Hakak, 2006). GPR43 was also found to be upregulated in islets from db/db and ob/ob mice. These findings need, however, to be studied in more detail.

5.3 GPR119

The fatty-acid-binding receptor GPR119 is expressed in islets (Chu et al., 2007; Sakamoto et al., 2006). The expression level of GPR119 is high in isolated mouse islets, and using a polyclonal antibody in immunohistochemical analysis of pancreas, GPR119 has been suggested to be located in β cells and in PP-cells (Chu et al., 2007, Sakamoto et al., 2006). Activation of GPR119 by lysophosphatidylcholine (Soga et al., 2005) and oleoylethanolamide (OEA) (Overton et al., 2006) have been shown to stimulate insulin secretion through increased formation of cAMP (Soga et al., 2005). Interestingly, it has also been reported that GPR119 may mediate glucose-stimulated insulin secretion (Chu et al., 2007; Sakamoto et al., 2006; Soga et al., 2005). GPR119 expression has also been shown to be elevated in islets from diabetic db/db mice (Soga et al., 2005). It is currently not known whether GPR119 is expressed in α cells and whether it plays a role in glucagon secretion.

5.4 GPR120

GPR120 is another orphan GPCR that was recently found to be activated by fatty acids (Hirasawa et al., 2005). However, whereas GPR120 is abundantly expressed in the intestine, where its activation results in release of GLP-1, it is not expressed in the pancreas or clonal ß cells (MIN6) (Katsuma et al., 2005). GPCR120 is therefore only indirectly involved in the regulation of islet function, i.e., through GLP-1.

6. GIP and GLP-1 receptors

Specific GPCRs for the incretin hormones GIP and GLP-1 are of major importance for islet function (Drucker, 2005). Both these hormones potently augment glucose-stimulated insulin secretion through increased cAMP (Mayo et al., 2003; Moens et al., 1996).

6.1 GIP receptors

The GIP receptor has been identified in human pancreatic islets (Gremlich et al., 1995). GIP receptors, which are linked to G_s-protein, are predominantly expressed in β cells (Drucker, 2006). Furthermore, GIP has been shown to augment glucose-stimulated insulin secretion (Mayo et al., 2003; Moens et al., 1996) and to inhibit β cell apoptosis (Trümper et al. 2001). Furthermore, GIP also stimulates glucagon secretion, as demonstrated under euglycemic conditions in humans (Meier et al., 2003). However, whether GIP receptors are expressed in α cells is not known.

The role of GIP signaling in glucose homeostasis and insulin secretion has been demonstrated in mice lacking GIP receptors (GIPR-/-). These mice exhibit reduced glucose-stimulated insulin secretion after oral administration of glucose, which results in mild glucose intolerance (Miyawaki et al., 1999). However, the islet response to intraperitoneal glucose was normal, demonstrating that the GIP receptor is primarily involved in the incretin action. It

has been demonstrated that the effect of GIP in stimulating insulin secretion is impaired in type 2 diabetes (Vilsboll et al., 2002). The reason for this has recently been suggested to be secondary to hyperglycemia as demonstrated experimentally both in vivo (Xu et al., 2007) and in vitro (Zhou et al., 2007).

Due to the effects of GIP on β cell function, the GIP receptor may be a target for treatment. However, since GIP appears to be insufficient in stimulating insulin secretion in subjects with diabetes (Nauck et al., 1986; Vilsboll et al., 2002), GIP does not appear as a rationale treatment for the disease (Meier & Nauck, 2004).

6.2 GLP-1 receptors

The GLP-1 receptor is expressed in islet β and δ cells. Whether the receptor is expressed on α cells is controversial. One study demonstrated GLP-1 receptors in rat pancreatic islets α, β and δ cells (Thorens, 1992), while others have been unable to detect the receptor in α cells (Fehmann and Habener, 1991). It is possible that this discrepancy is due to the fact that GLP-1 receptors seem expressed only in a subpopulation of the α cells (Heller & Aponte, 1995). Like the GIP receptor, also the GLP-1 receptor couples to $G_{\alpha s}$ with subsequent activation of adenylate cyclase and elevation of cAMP levels. Activation of the GLP-1 receptor stimulates insulin secretion and inhibits glucagon secretion and has also long-term effects in that it stimulates β cell proliferation and inhibits apoptosis (Farilla et al., 2003). GLP-1 receptor activation leads to the activation of PKB and increased expression of pancreas duodenal homebox-1 (Pdx1), two factors which have been suggested to be involved in islet proliferation and cyto-protection (Drucker, 2003; Li et al., 2005; Perfetti & Hui, 2004).

GLP-1 is important in glucose homeostasis and energy metabolism. Studies on mice where the receptors have been inactivated, either by a pharmacological substance or through genetic mutations, have demonstrated reduced insulin secretion after oral administration of

glucose in association with impaired glucose tolerance (Drucker 2005, Scrocchi et al. 1996). Mice lacking the GLP-1 receptor are hyperglycemic, while glucagon levels and food intake were not altered, suggesting that there are mechanisms compensating for the lack of GLP-1 receptors (Scrocchi et al., 1996). One compensatory mechanism could be GIP, and therefore double incretin receptor knockout (DIRKO) mice have been studied. These mice have impaired but not completely absent insulin response to oral glucose, showing that also other mechanisms contribute (Hansotia et al., 2004). Interestingly, the DIRKO mice have also impaired insulin secretion to parenterally administered glucose, which shows that the GLP-1 and GIP receptors are important for a normal glucose competence in the β cells.

One novel diabetes treatment strategy is to activate GLP-1 receptors (Drucker and Nauck, 2006). Two well-studied GLP-1 receptor agonists are exendin-4 (exenatide) and liraglutide (Drucker and Nauck, 2006). Exenatide has been shown to efficiently reduce HbA_{1c} in combination with metformin or a sulphonylurea and to reduce body weight (Drucker and Nauck 2006). Exenatide (Byetta®) is now approved for treatment in the US and in Europe. Furthermore, clinical trials have demonstrated that liraglutide also reduces HbA_{1C} in type 2 diabetics (Nauck et al., 2006).

Another strategy of GLP-1-based treatment is to inhibit GLP-1 degradation by inhibition of dipeptidyl peptidase 4 (DPP-4) (Ahrén, 2007; Drucker and Nauck, 2006). DPP-4 inactivates GLP-1, which will prolong the concentration of GLP-1 after each meal, taking advantage of the antidiabetic islet effects of the hormone. Several small-molecule DPP-4 inhibitors have been developed and examined in clinical trials (Ahrén, 2007). Two of these inhibitors, sitagliptin (Januvia®) and vildagliptin (Galvus®) are now approved as a drug for the treatment of type 2 diabetes in combination therapy in Europe, and Januvia® is approved also in the US.

7. Neurotransmitter receptors

Islets are richly innervated by parasympathetic, sympathetic and sensory nerves, with several neurotransmitters and neuropeptides stored in the nerve terminals (Ahrén et al., 2006) (Table 1). Activation of the parasympathetic nerves enhances insulin secretion and it is particularly important for the so-called cephalic phase, which occurs prior to the elevation of plasma glucose levels (Ahrén & Holst, 2001). The four major neurotransmitters located in the parasympathetic nerves are acetylcholine (ACh), vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase activating polypeptide (PACAP) and gastrin releasing peptide (GRP). They all interact with the islet cells via GPCRs, stimulating both insulin and glucagon secretion. The sympathetic nerves contain noradrenaline, galanin and neuropeptide Y (NPY). Activation of the sympathetic nerves inhibits both basal and glucose-stimulated insulin secretion and stimulates glucagon secretion (Ahrén et al., 2006). The sensory nerves contain calcitonin gene-related peptide (CGRP). The role of the sensory nerves in islet function is not well known, but it has been suggested that CGRP inhibits glucose-stimulated insulin secretion (Ahrén & Pettersson, 1990). Cholecystokinin (CCK) is another neuropeptide that has been found in islet nerves. Since CCK is a potent stimulator of insulin section it is possible that CCK has insulinotropic action through the activation of CCK receptors on the β cells (Karlsson & Ahrén, 1992). All these neurotransmitters signal through specific GPCRs and regulate insulin secretion through several pathways (Fig. 2).

7.1 PAC_1, $VPAC_1$, and $VPAC_2$ receptors

The receptors for PACAP and VIP are of three different subtypes, PAC_1, $VPAC_1$, and VPAC2, and of these at least PAC_1 and $VPAC_2$ are expressed in the β cells (Borboni et al., 1999). These receptors are linked to the G_s-protein with subsequent elevation of cAMP and

stimulation of insulin secretion (Filipsson et al., 2001). Disruption of the PAC_1 receptor in mice results in impaired insulin secretion after PACAP administration (Jamen et al. 2000). However, these mice also display reduced glucose-stimulated insulin secretion following both oral and intravenous glucose administration, which suggests that the PAC_1 receptor are important for the effect of glucose (Jamen et al., 2000). Furthermore, $VPAC_2$-/- mice exhibit reduced insulin secretion but maintained glucose tolerance after intravenous administration of glucose, suggesting peripheral effects on insulin sensitivity (Asnicar et al., 2002). Furthermore, PACAP and VIP both stimulate glucagon secretion as has been demonstrated both in humans, in animals and in vitro (Filipsson et al. 2001).

7.2 Adrenergic receptors

Both β_2- and α_2-adrenoceptors are expressed in the islets. Noradrenaline has been shown to stimulate insulin and glucagon secretion through the β_2-adrenergic receptors (Kuo et al., 1973, Ahrén 2000). At the same time, noradrenaline also interacts with α_2-adrenoceptors, which results in the inhibition of insulin secretion and the stimulation of glucagon secretion (Ahrén 2000). Therefore, catecholamines may affect insulin secretion both as stimulators through β_2-adrenoceptors and as inhibitors through α_2-adrenoceptors (Ullrich & Wollheim 1985). The adrenoceptors are GPCRs; β_2-adrenoceptors are linked to activation of cAMP whereas α_2-adrenoceptors are linked to inhibition of cAMP production and opening of K^+ channels. Three subtypes of the α-adrenoceptors have been described, called α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors. A recent study explored which of those that is of relevance for the inhibition of insulin secretion by using selective knockout mice (Peterhoff et al., 2003). It was found that adrenaline did not inhibit insulin secretion in mice with a double knockout of α_{2A}- and α_{2C}-adrenoceptors, and that the inhibition of insulin secretion by adrenaline was partially reduced in mice with single knockout of these receptors. This suggests that these two subtypes of the

α_2-adrenoceptors mediate the inhibition of insulin secretion by catecholamines. Conversely, transgenic mice with β-cell-specific overexpression of α_{2A}-adrenoceptors displayed reduced glucose-stimulated insulin secretion and impaired glucose tolerance (Devedjian et al., 2000), which further supports the relevance of these receptors. Several potential strategies are possible for the development of adrenoceptors as drug targets in type 2 diabetes; however, these strategies are problematic due to systemic effects of adrenoceptor agonists and antagonists. One interesting approach is to administer α-adrenoceptor inhibitors, which would increase insulin secretion. This strategy has been successful in a pilot experiment (Broadstone et al. 1987).

7.3 CCK receptors and muscarinic receptors

Both CCK and muscarinic agonists stimulate insulin and glucagon secretion via coupling to G_q, which activates PLC (Fig 2). Two CCK receptor subtypes exist (CCK_A- and CCK_B-receptors) and five different muscarinic receptor subtypes exist. The GPCRs that are involved in the islet actions of CCK and acetylcholine has been shown to be the CCK_A receptor and, the M_3 muscarinic receptor subtypes, respectively (Karlsson & Ahrén, 1992, Ahrén 2000). The role of CCK_A receptors for islet function remain to be established. On study demonstrated that infusion of CCK stimulates insulin secretion in subjects with type 2 diabetes (Ahrén et al. 2000), which would suggest a potential of developing islet specific CCK_A receptor agonists in the treatment. The physiological role of the M_3-muscarinic receptors was recently explored in a study using beta cell specific M_3-receptor knockout and beta cell specific M_3 overexpression in mice (Gautam et al. 2006). It was found that mice with M_3 muscarinic receptor knockout had reduced insulin secretion and impaired glucose tolerance, whereas M_3 muscarinic transgenic mice had increased insulin secretion and glucose tolerance. Therefore, M_3 muscarinic receptors are of profound importance for β-cell function, both as mediating the cholinergic

neurotransmission, which is of importance after meal ingestion and as being of importance for the glucose competence of the β cells. M_3 muscarinic receptor activation would therefore be a drug target candidate for the treatment of islet dysfunction in type 2 diabetes. Indeed, it has been demonstrated that treatment of glucose intolerant high-fat fed mice with cholinergic agonism normalizes glucose tolerance and insulin secretion (Ahrén et al. 1999). However, this strategy has serious drawbacks due to general cholinergic effects, and therefore it has to await development of β cell specific M_3 muscarinic receptor agonists.

7.4 NPY receptors

NPY is a neurotransmitter, which is localized to the autonomic sympathetic nerve terminals in the islets (Ahrén et al. 2006). Several different NPY receptors exist, designated Y1, Y2, Y3, Y4, Y5 and Y6, which all are GPCRs (Cox et al. 2007). NPY inhibits insulin secretion and receptor studies have shown that this effect is mediated by the NPY Y1 receptors (Morgan et al. 1998). This effect is mediated through inhibition of adenylate cyclase activity, presumably by G_i. This finding is supported by studies showing that the islet β cells express the Y1 receptors (Cho & Kim 2004). On the other hand, mice with NPY Y1 receptor gene knockout have normal glucose-stimulated insulin secretion, showing that these receptors are not involved in the insulin response to glucose (Burcelin et al. 2001). In addition, NPY has been shown to promote β cell replication (Cho and Kim 2004). Due to its inhibitory action on insulin secretion, Y1 receptors are not an appropriate target for treatment of diabetes.

8. Glucagon and somatostatin receptors

The islet hormones glucagon and somatostatin affect β cell function through paracrine effects within the islets: glucagon stimulates insulin secretion whereas somatostatin inhibits insulin secretion. Both hormones work through GPCRs.

8.1 Glucagon receptors

Glucagon plays a key role in maintaining circulating glucose levels mainly through its stimulation of hepatic glucose production (Cherrington et al., 1978; Jiang & Zhang, 2003). Glucagon receptors (Gcgr) are also expressed on pancreatic β cells and glucagon stimulates insulin release (Kieffer et al., 1996; Jiang & Zhang 2003). Islets are dependent on signaling through the glucagon receptors and a sufficient elevation of cAMP for normal glucose responsiveness (Huypens et al., 2000). The glucagon receptor is a GPCR and binding of glucagon results in the activation of the $G_{s\alpha}$ and G_q proteins (Jiang & Zhang, 2003). Evidence supporting the idea that glucagon is important for the insulin response to glucose is that islets rich in glucagon have increased sensitivity to glucose, secreting more insulin than islets containing fewer α cells (Pipeleers et al., 1985).

To study the physiological contribution of glucagon receptors for islet function, mice lacking glucagon receptors (Gcgr-/-) have been generated. These mice display low circulating glucose levels (Gelling et al., 2003). They have also improved glucose tolerance, observed after oral and intravenous glucose administration (Sorensen et al., 2006). This probably reflects the systemic deletion of the glucagon receptors rather than the deficiency in the β cells. Hence, the contribution of glucagon receptors for β cell function remains to be established. Since glucagon levels are often elevated in type 2 diabetes (Reaven et al., 1987), hyperglucagonemia may contribute in maintaining hyperglycemia in these individuals. Particularly when insulin levels are low or during insulin resistance, hyperglucagonemia results in increased hepatic glucose production (Basu et al., 2005; Larsson & Ahrén, 2000). Therefore, inhibition of the glucagon signal has been suggested as a target for the treatment of type 2 diabetes (Sloop et al., 2005). However, this applies to extra-islet receptors, since inhibiting glucagon receptors within the islets would lead to, if anything, impaired insulin secretion. This would, however,

not be of major concern, as recently demonstrated in a study using a small-molecule glucagon receptor antagonist in mice with high-fat-diet-induced insulin resistance. It was found that chronic inhibition of the glucagon signal resulted in reduced glycemia and improved islet function, as well as improved insulin sensitivity (Winzell et al., 2007).

8.2 Somatostatin receptors

Five different somatostatin receptors exist in humans ($sstr_1$, $sstr_{2b}$, $sstr_3$, $sstr_4$ and $sstr_5$ receptors), of which all are GPCRs (Viollet et al. 1995). All these receptors have been shown to be expressed in β cells (Portela Gomes et al. 2000). Studies in knockout mice have shown that it is the $sstr_2$ subtype which is the receptor subtype that mediates the inhibition of insulin and glucagon secretion by somatostatin (Strowski et al. 2000). This receptor subtype couples to G_i/G_o proteins, which results in inhibition of adenylate cyclase activity, although it has been shown that the inhibitory effect of somatostatin is more complex and also involves other mechanisms (Renström et al. 1996). Since somatostatin inhibits insulin secretion, it has not been used in the treatment of diabetes; however, activation of sstr (by the somatostatin analogue octreotide) has been developed as a treatment of exaggerated insulin secretion in insulinomas and other types of hyperinsulinemia (Lamberts et al. 1996).

9. Novel GPCRs expressed in islets

9.1 GPR54

Kisspeptin belongs to a family of peptides that has been identified as ligands to GPR54, which couples to G_q and the PLC pathway (Kotani et al., 2001; Messager et al., 2005). The gene from which kisspeptins are transcribed, *KISS1*, is a tumor-suppressor gene in breast cancer cells, but later work has also identified products of this gene as an energy sensor (Lee et al., 1996). Earlier studies showed that GPR54 is expressed in hypothalamic neurons as well as

in the pancreas and the placenta (Kotani et al., 2001). It was recently shown that both GPR54 and kisspeptin are expressed in mouse and human islets and that the receptor is expressed both in α and β cells (Hauge-Evans et al., 2006). Furthermore, the addition of kisspeptin to isolated islets potentiates glucose-stimulated insulin secretion, while the peptide has no effect on glucagon secretion (Hauge-Evans et al., 2006). However, the involvement of this receptor in islet physiologic remains to be established.

9.2 Cannabinoid receptors

Cannabinoid receptors are GPCRs, which are expressed mainly in the brain (Xie et al., 2007). The CB_1 receptor binds Δ^9-tetrahydrocannabinol and the receptor is coupled to $G_{\alpha i}$. The cannabinoid system has been suggested to be involved in the regulation of food intake; antagonism of the CB_1 receptor and deletion of CB_1 receptors reduce food intake and body weight (Cota et al., 2003, Xie et al. 2007). Recently, CB_1 receptors (and also CB_2 receptors) were shown to be expressed in islets, and activation of these receptors was found to inhibit insulin secretion through a Ca^{2+}-dependent mechanism (Juan-Pico et al. 2006). It has also been demonstrated in vivo that CB_1 receptor activation by anandamide induces glucose intolerance in rats and that this effect is reversed by a CB_1 receptor antagonist (Bermudez-Siva et al 2006). Hence, CB_1 receptors may be targets also for affecting islet function in diabetes.

9.3 Vasopressin receptors

The effects of vasopressin are linked to four types of GPCRs, called $V1_A$, $V1_B$, V2 and OT (oxytocin) receptors (Birnbaumer 2000). The $V1_A$ vasopressin receptor has been studied in most detail and found to couple to G_q and to activate PLC. Vasopressin is known to stimulate the secretion of both insulin and glucagon (Dunning et al. 1984). Recent studies have ex-

plored the receptor subtype responsible for these islet actions. Binding studies have thereby shown that $V1_B$ binding exists on pancreatic islets, and, furthermore, mice with genetic deletion of $V1_B$ receptors display lost insulinotropic action of vasopressin (Oshikawa et al. 2004). Therefore, vasopressin-induced islet actions seem mediated by the $V1_B$ receptor.

9.4 Purinergic receptors

It is known that islets express two types of pruinergic receptors, which are GPCRs: these receptors are P_1 receptors (activated by adenosine) and P_2 receptors (activated by ATP and ADP) (Hillaire-Buys et al. 1994). P_2 receptor activation stimulates insulin secretion through a Ca^{2+}-dependent mechanism, whereas P_1 receptor activation inhibits insulin secretion through inhibition of adenylate cyclase (Hillaire-Buys et al. 1994). Further studies have shown that it is the P_{2Y} receptor subtype of the purinergic P_2 receptor complex that is expressed in islets, and that in rats, a selective P_{2Y} receptor agonist stimulates insulin secretion (Chevassus et al. 2002). This has suggested the P_{2y} purinergic receptor as a good target for treatment of diabetes. Further subtyping of these receptors have shown that 6 different P_{2Y} receptors exist, and functional characterization in clonal β cells has shown that it is P_{2Y1} subtype which is implicated in the β cell effects (Lugo-Garcia et al. 2007). P_{2Y} receptors are now tested as a potential drug target for diabetes (Williams & Jarvis 2000). In particular, a group of P_{2Y} receptor agonists have shown promising effects in experimental studies (Fischer et al. 1999).

10. Other GPCRs involved in energy balance

Several GPCRs have been shown to be involved in the regulation of energy homeostasis and therefore having a potential of influencing islet function, but without being shown to be expressed in islets.

10.1 GPR103

A potential novel peptide for the regulation of islet function is the orexigenic neuropeptide 26Rfa, which is a ligand to GPR103. In the perfused rat pancreas, 26Rfa has been found to inhibit insulin secretion, but to have no effect on glucagon secretion (Egido *et al.*, 2007). Despite the significant effect of 26Rfa on insulin secretion, however, GPR103 has not been detected in islet cells and thus the signaling mechanism is still unknown.

10.2 GPR30

Evidence has recently been put forward suggesting that estrogen may play a role in islet function (Le May et al., 2006). The classical estrogen receptors (Erα and Erβ) are localized in the cytosol or in the nucleus of a cell. However, there is growing evidence suggesting that membrane-bound receptors for estrogen also exist, because estrogen mediates rapid effects that cannot be explained by transcriptional regulation but by a membrane-bound receptor (Prossnitz et al., 2007). The signaling events caused by estrogen are elevation of cAMP, Ca^{2+} release and activation of protein kinases. Recently, the GPCR GPR30 was suggested to be an estrogen receptor (Filardo et al., 2007; Filardo et al., 2000; Kanda & Watanabe, 2003). It has been shown that estrogen protects islets from apoptosis (Le May et al., 2006) and it is therefore possible that GPR30 may be involved in the regulation of islet mass. However, whether GPR30 is expressed in islets is currently not known.

10.3 GPR12

GPR12 is expressed in the central nervous system and two ligands have been identified: sphingosine 1 phosphate and sphingosylphosphorylcholine (Ignatov et al., 2003). To evaluate whether GPR12 plays a role in metabolism, GPR12-deficient mice were studied. These mice were found to be obese and dyslipidemic with reduced energy expenditure and decreased res-

piratory quotient, while food intake was not different from wild-type mice (Bjursell et al., 2006). Basal insulin levels were reduced and glucose was elevated, suggesting that GPR12 is needed for glucose homeostasis. However, GPR12 does not seem to be expressed in islets. Therefore, the exact involvement of GPR12 in glucose homeostasis remains, however, to be studied.

10.4 GPR39

GPR39 is a GPCR that belongs to the ghrelin receptor family and it is highly expressed in the gastrointestinal tract in mice and in humans (McKee et al., 1997). The identity of the endogenous ligand for GPR39 is still elusive. Obestatin, which is a peptide derived from the ghrelin precursor, was recently suggested as a ligand for GPR39 (Zhang et al., 2005). However, later studies were unable to repeat the results (Holst et al., 2007; Lauwers et al., 2006). Instead, Zn^{2+} was suggested as a ligand for GPR39 (Holst et al., 2007). Activation of GPR39 increases cAMP accumulation and IP_3 turnover, suggesting that both the G_s and G_q pathways are involved. However, at present it is not known whether GPR39 is expressed in islets, and further studies are required to establish the role of obestatin in islet function.

11. Summary

The GPCRs have attracted considerable attention due to their potential as targets in novel drug development, and the orphan GPCRs where the ligands have still not been identified are of particular interest. Many GPCRs are expressed on islet cells and they are involved in the regulation of islet hormone secretion and have the potential of being candidates as drug targets for the treatment of type 2 diabetes. Currently, the most promising novel drug target is the GLP-1 receptor, which upon activation has multiple positive effects in that it stimulates insulin secretion and inhibits glucagon secretion. There are yet many more targets to be iden-

tified and both GPCRs with known ligands as well as the orphan GPCRs need to be studied with regard to tissue localization and ligand specificity to be evaluated as possible novel drug targets for treatment of type 2 diabetes. Most promising are M_3 muscarinic receptors and P_{2y} receptors.

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Table 1 Hormones, neurotransmitters, neuropeptides and nutrients that affect insulin secretion via interaction through GPCRs.

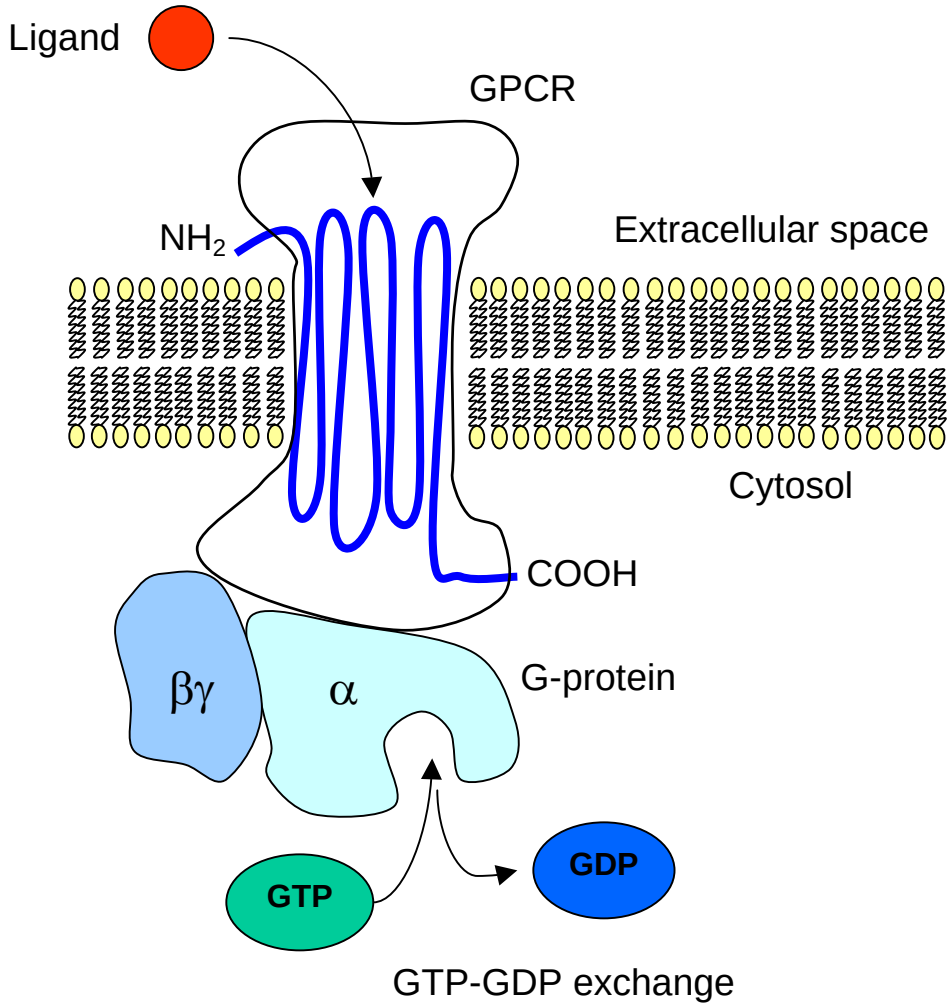
Ligand	**Receptor**	**Effect on insulin secretion**	**Effect on glucagon secretion**	**G protein**
Acetylcholine	M_3	Stimulatory	Stimulatory	G_q
ATP/ADP	P_{2Y}	Stimulatory	Not known	G_s
Cannabinoids	CB_1	Inhibitory	Not known	G_i
CCK	CCK_A	Stimulatory	Stimulatory	G_q
FFAs	GPR40, GPR119	Stimulatory Stimulatory	Stimulatory Not known	G_q G_s
Glucagon	Gcgr	Stimulatory	Stimulatory	G_s, G_q
GLP-1	GLP-1R	Stimulatory	Inhibitory	G_s
GIP	GIPR	Stimulatory	Stimulatory	G_s
Kisspeptin	GPR54	Stimulatory	No effect	G_q
NPY	Y_1	Inhibitory	Stimulatory	G_i
Noradrenaline	β_2 α_2	Stimulatory Inhibitory	Stimulatory Stimulatory	G_s G_i
Somatostatin	$sstr_2$	Inhibitory	Inhibitory	G_o/G_i
PACAP	PAC_1	Stimulatory	Stimulatory	G_s
Vasopressin	V_{1B}	Stimulatory	Stimulatory	G_q
VIP/PACAP	$VPAC_2$	Stimulatory	Stimulatory	G_s

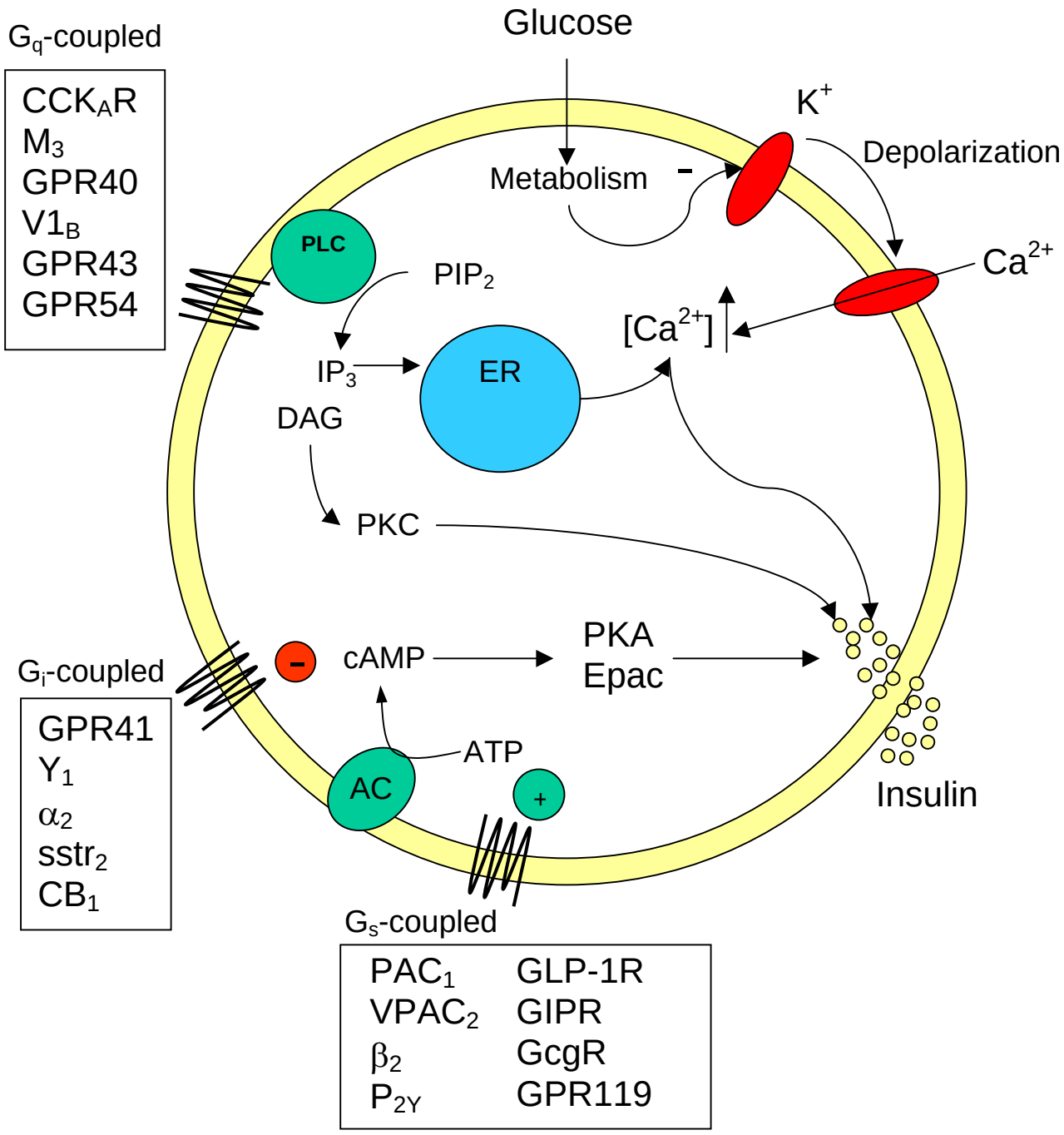
Figure legends

Fig. 1. Schematic representation of a GPCR with the seven transmembrane protein which is coupled to an intracellular G protein. The G-protein consists of three subunits α, β and γ. Upon GPCR activation, guanosine diphosphate (GDP) is exchanged against guanosine trisphosphate (GTP), which dissociates the G-protein complex into two units, the α and the βγ subunits. These subunits in turn activate or inhibit enzymes.

Fig. 2. Schematic representation of islet GPCRs and their main secretory signaling pathways in the β-cells. For more detailed description, see text. Potential genomic effects are overlooked in the figure.

Fig 1


Ligand
GPCR
NH2
Extracellular space
Cytosol
COOH
βγ
α
G-protein
GTP
GDP
GTP-GDP exchange


Glucose
G_q-coupled
CCK_AR
M_3
GPR40
$V1_B$
GPR43
GPR54
K^+
Depolarization
Metabolism
PLC
PIP_2
Ca^{2+}
$[Ca^{2+}]$
IP_3
ER
DAG
PKC
G_i-coupled
GPR41
Y_1
α_2
$sstr_2$
CB_1
cAMP
PKA
Epac
ATP
AC
Insulin
G_s-coupled
PAC_1
$VPAC_2$
β_2
P_{2Y}
GLP-1R
GIPR
GcgR
GPR119