Recent Advancement in Treatment of Type-II Diabetes Mellitus: A Review

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ABSTRACT
Type 2 diabetes mellitus has become a major cause of concern due to changing diet habits and lifestyle. Though a wide range of drugs are available to treat this disease, a need for newer, still safer drugs is being felt nowadays, hypoglycemia being the major concern in the use of presently available drugs. Accordingly, newer areas are being exploited and the huge research done has given some fruitful results. This review focuses on these recent developments to treat type 2 diabetes mellitus. In 2010 12.1 million people were estimated to be living with diabetes in Africa, and this is projected to increase to 23.9 million by 2030. These include DPP IV inhibitors, glucokinase activators and G protein coupled receptors as potential drug targets. Dipeptidyl peptidase IV (DPP IV), an enzyme which degrades incretins, can be inhibited to increase the incretin level. Incretins have insulinotrophic action and this is the rationale behind using DPP IV inhibitors. Glucokinase, a glucose phosphorylating enzyme, converts glucose to glucose-6-phosphate and thus makes it available for entry into pathways of glucose metabolism like the tricarboxylic acid pathway. Metformin more effective than the other drug therapy. Thus drugs which can activate glucokinase can help reduce free glucose in blood and favour its metabolism.

Keywords: T2D, DPP IV, Glucokinase Activator, GPCR.

INTRODUCTION
Type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus; often abbreviated to NIDDM or T2D), which comprises approximately 90–95% of all diabetes cases, is a chronic metabolic disorder involving the dysregulation of glucose metabolism, b-cell dysfunction and impaired insulin sensitivity. It is becoming more prevalent because of the recent dramatic rise in obesity levels¹². It is also now being diagnosed in children and adolescents.³ It is estimated that >180 million people worldwide have diabetes mellitus; this figure is expected to more than double by the year 2030⁴. The increasing prevalence of diabetes is of concern because of the morbidity and mortality associated with the disease. T2D is associated with several complications, for example (i) macrovascular complications⁵,⁶ resulting from hyperlipidemia and hypertension, which can lead to end-stage renal disease, limb amputation and accelerated atherosclerosis (cardiovascular disease)⁷,⁸ and (ii) chronic microvascular complications⁹ such as retinopathy (blindness), nephropathy and neuropathy. Diabetic foot syndrome is an important complication of diabetes, related to elevated protease activity in wounded tissue which causes high rates of wound infection and healing problems. In contrast to normal wounds, poorly healing diabetic wounds exhibit prolonged inflammation, which generates correspondingly intensified metalloprotease and neutrophil elastase responses⁹. In 2010 12.1 million people were estimated to be living with diabetes in Africa, and this is projected to increase to 23.9 million by 2030⁴. As of 2010, an estimated 280 million people had diabetes, with type 2 making up about 90% of the cases globally¹¹. While several options are currently available for the treatment of T2D. These include glucosidase inhibitors, biguanides, meglitinides, sulfonylureas, thiazolinedines, insulin, amylin agonist and glucagon like peptide-1(GLP-1) analogues (eg. Exenatide). But no single marketed drug is capable of achieving long-lasting blood glucose control in the majority of T2D patients.¹⁰ Therefore, the use of initial monotherapy may have to be expanded to complex combination therapies as the disease progresses¹¹. The present article provides a brief overview on DPP IV inhibitors, glucokinase activators and islets GPCR as potential targets for T2D treatment. 1.2 Dipeptidyl Peptidase- IV ( Dpp – Iv) Inhibitors Recent T2D medications utilize the incretin gut hormone pathway, a focus of scientific and clinical research for decades.¹² The so-called insulin effect, known today as the incretin effect¹³ i.e., greater insulin secretion in response to nutrient ingestion—was identified in 1964 when Elrick et al⁴ demonstrated that orally administered glucose produced a significant and sustained increase in plasma insulin, whereas intravenously administered glucose

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produced a smaller and transient insulin increase. The two most well-characterized incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP). GLP-1 and GIP are incretins released from the gut in response to food and play an essential role in maintaining glucose homeostasis. Together, they are responsible for up to 70% of insulin secreted following a meal. Currently, therapeutic agents, acting as either an incretin mimetic (via GLP-1 analogs) or to inhibit the breakdown of GLP-1 (via dipeptidyl peptidase-4 [DPP-4] inhibitors or glytns) are available for treatment. Inhibition of DPP-IV has been shown to improve glucose tolerance in these patients by enhancing the insulino tropic effects of GLP1. Dipeptidyl peptidase-IV (DPP-IV), a serine protease degrades a number of biological peptides including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP). In addition to and independent of its enzymatic activity in plasma, DPP-4 is a membrane-spanning peptidase that is widely distributed in numerous tissues and T-cells, B-cells, and natural killer cells. DPP-4 serves as a T-cell costimulator, playing a functional role in T-cell activation and proliferation. There are three general classes of DPP-4 inhibitors: (1) reversible substrate analogs; (2) covalently modifying substrate analogs; (3) reversible non-peptide heterocyclic compounds. These inhibitors are amide derivatives of pyrrolidine or thiazolidine, which bind with even greater affinity. Many drugs are recently known to inhibit DPP-4. Metformin, thiazolidinediones (rosiglitazone, troglitazone), sulfonylureas (glybenclamide, tolbutamide), and meglitinides (nateglinide) have their mechanism of action.

**Mechanism of Action**

These new drugs act by increasing the level of incretins. Two approaches are to enhance GLP-1 effects in vivo by administration of agents that mimic the effects of the incretins but are resistant to degradation by DPP-4 (eg, exenatide) and agents that prevent incretin degradation. Sitagliptin enhances the effects of the incretins by DPP-4 enzyme inhibition. Thus, following administration of sitagliptin, postprandial levels of active GLP-1 are increased. There is an increase in insulin release and decrease in glucagon secretion from the pancreatic cells. Activation of GIP and GLP-1 receptors on pancreatic cells leads to increased levels of cyclic AMP and intracellular calcium. This results into insulin secretion. Also, activation of GIP and GLP-1 receptors results in resulting in enhanced cell function due to cell resistance to apoptosis, proliferation, and neogenesis.

**Glucokinase Activators**

Glucokinase (GK, GLK, hexokinase IV or hexokinase D) is a glucose phosphorylating enzyme which catalyzes the first step of glucose metabolism (conversion of glucose to glucose-6-phosphate). It is an attractive target for Type 2 diabetes. It is a 50-kDa cytoplasmic enzyme. GK is found in pancreatic beta cells and liver parenchymal cells. These cells have important role to play in glucose metabolism.

**Glutaminase Inhibitors**

Glutaminase is a glutaminase that catalyzes the removal of glutamine from amino acids. It is a target for Type 2 diabetes.

**DPP-4 Inhibitors**

DPP-4 inhibitors are a class of drugs that inhibit the degradative activity of DPP-4, which is a serine protease that is widely distributed in numerous tissues and T-cells, B-cells, and natural killer cells. DPP-4 serves as a T-cell costimulator, playing a functional role in T-cell activation and proliferation. There are three general classes of DPP-4 inhibitors: (1) reversible substrate analogs; (2) covalently modifying substrate analogs; (3) reversible non-peptide heterocyclic compounds. These inhibitors are amide derivatives of pyrrolidine or thiazolidine, which bind with even greater affinity. Many drugs are recently known to inhibit DPP-4. Metformin, thiazolidinediones (rosiglitazone, troglitazone), sulfonylureas (glybenclamide, tolbutamide), and meglitinides (nateglinide) have their mechanism of action.
transporter in the pancreatic beta cells and liver parenchymal cells. Under physiological glucose concentrations, this process is not rate limiting to the overall rate of glucose uptake in these cells. The rate of phosphorylation of glucose to G-6-P limits the rate of glucose uptake. This phosphorylation is catalyzed by GK (GKB in pancreatic b-cells and GKL in liver). Under normal physiological conditions and concentrations, GK can only phosphorylate glucose if the concentration of glucose is above 1–2 mM. K_0.5 (6–10 mM) of GK shows that it has a low affinity for glucose. Phosphorylation of glucose leads to glycogen synthesis in liver and glycolysis. This converts glucose into pyruvate in pancreatic beta cells. The increase of the TCA and electron transport increases ATP/ADP ratio. This causes the closure of ATP-sensitive K+ channels, followed by membrane depolarization and subsequently Ca2+ influx. This causes the release of insulin from beta cells into the circulation. GK activity and its intracellular location are under regulation of a protein produced in hepatocytes called glucokinase regulatory protein (GKRP). GK can be activated either directly (glucose utilization in both liver and pancreas is stimulated) or by destabilizing the GK–GKRP complex (exclusive action in liver). In T2D there is impaired glucose utilization in both tissues. Hence, both types of compounds may be useful for the treatment of T2D. Loss of function mutations in GK gene cause maturity-onset diabetes of the young type 2 (MODY-2) and permanent neonatal diabetes mellitus (PNDM). Hyperglycemia in MODY-2 patients results from defective glucose utilization in both the pancreas and liver which is a result of raised threshold for glucose stimulated insulin secretion. Conversely, activating mutations of GK in humans produce hypoglycemia and hyperinsulinemia. Thus, the activation of GK upregulates insulin (from the pancreas) and promotes glucose storage as glycogen in the liver under elevated blood glucose conditions. This may prove to be a promising approach for the development of treatments for T2D. The risk of hypoglycemia is low with GK activators as they have no effect on GSIS at low glucose concentrations. Conversely, at low glucose concentrations, GKAs are able to stimulate those cellular processes that would normally take place only at significantly higher glucose levels. The distance between the allosteric site of GK (where GK activators bind) and the glucose binding site is about 20Å. Recent studies suggest that GK activators have potent antihyperglycemic actions in rodents. This is due to increase in pancreatic insulin secretion and enhanced hepatic glucose metabolism. An enzyme, 6-phosphofructo-2-kinase/ fructose-2,6-bisphosphatase was found to be an activator of GK. Conformational change enhances the catalytic action of GK i.e. the enzyme exists in different forms that interconvert slowly as a result of substrate binding. As the rate of interconversion is slow as compared to the catalytic cycle, one form is predominant at steady state and leads to positive kinetic cooperativity. This traditional enzyme kinetics characterization of GK cooperativity has recently been supported by the cocrystallization of a GKA–GK complex and the demonstration of superopen, open and closed conformations of the enzyme. GK possesses two catalytic cycles the ratio of which is responsible for the sigmoidal response to glucose (But some say that there is a single catalytic cycle). A slow catalytic cycle results at low glucose concentrations when the ‘superopen’ low affinity conformation is favored. Binding of the glucose substrate to GK, however, induces the formation of ‘open’ and ‘closed’ structures that are activated catalytic forms of GK. In other words, high glucose concentration favors the ‘open’ and ‘closed’ high affinity conformations that are associated with a fast catalytic cycle. GKAs stabilize the ‘open’ and ‘closed’ high affinity conformations, thereby activating GK for catalysis. The allosteric pocket at the hinge region is not formed in the ‘superopen’ conformation and is not accessible to GKAs for binding. This is the basis for the selectivity displayed by GKAs that increases the affinity of GK for glucose through selectively stabilizing the high affinity conformations of the enzyme. Nevertheless, GKAs also elicit Glucose Stimulated Insulin Secretion via indirect (i.e. noncatalytic) GK-dependent mechanisms, although the possibility of insulinotropic effects of GKAs independent of their kinetic effects on GK is believed to be entirely conjectural. In hepatocytes, the GKRP binds to the superopen form of GK thereby inhibiting GK activity. Binding of a GKA to the ‘open’ and ‘closed’ conformations of GK, however, prevents relaxation to the superopen form and activates GK for catalysis. Recently, it has been proposed that the GKRP–GK complex dissociates as GKAs bind to the allosteric site. In theory GKAs could activate GK either directly or by destabilizing the GKRP–GK complex. As a result of recent knowledge about crucial role of GK in glucose homeostasis, several GKAs have been reported during the past few years. GK activators have become an important area of focus of many pharmaceutical companies. Following are the few compounds which have been discovered to have GK activating activity:

1. A phenylacetamide derivative was reported as an orally active GKA that activated GK in a dose-dependent manner. It has become clinically effective due to the cardiovascular complications that it gave rise to. It did not affect other hexokinases of brain and muscle. Significant decrease in the elevation of glucose in an oral glucose tolerance test (OGTT) in rat models of diabetes was observed.

2. A novel class of substituted amino benzamides yielded substituted pyridine carboxamides and heteroaryl carboxybenzenes was also developed.

3. Benzamide-based activators: Several novel 1, 3, 5-trisubstituted benzenes have been reported as benzamide-based activators of GK. The thiophene derivative showed good in vitro potency. It also exhibited desirable antihyperglycemic effects in vivo.

4. Many urea derivatives have been reported as GK activators.

5. Acylecyclopropyl acetamide derivatives are also known to be good activators of GK.
6. AZD6370 is in phase 2 trials.[63] 
7. ID1101 [64] presently in phase 1 clinical studies has shown a good safety profile. In phase 1 clinical trials, ID1101 showed reduction in blood glucose and body weight. 
8. Compounds in preclinical studies include: TTP399 and ARRY403. ARRY403 also reduced both nonfasted and postprandial glucose in mice, without causing hypoglycemia or abnormal weight gain. 
9. Good glucose regulation, no weight gain and increased insulin content in pancreas was observed during preclinical results of compound NN9101. In human studies, reduction in both fasting and postprandial glucose was observed. 
10. ARRY588 showed glucose-lowering activity in a dose–response OGTT study[65,66]. 
11. PSN105 showed promising antihyperglycemic effects in diabetic animals[67]. 

The main question over the feasibility of GKA therapy is whether the same small molecule activators could modulate GK activity simultaneously in liver, pancreas and brain. It has been proposed that GKAs could be still more effective in combination with other anti-diabetic agents. Combining with an insulin sensitizer, such as a thiazolidinedione (TZD) may allow GKA to deliver enhanced glucose-lowering efficacy. The combination of GKAs with a sulfonylurea may help avoid the potential incidence of hypoglycemic effects. A combination of GKA/GLP1 (glucagon-like peptide 1) analogs or GKA/DPP4 (dipeptidyl peptidase 4) inhibitors could be helpful. Preclinical data for ARRY403 in combination with metformin, pioglitazone or sitagliptin (a DPP4 inhibitor) has been generated[65]. The possible problems for GKA therapy may include the excessive accumulation of liver glycogen or increased conversion of glucose into fatty acids and triacylglycerols (as observed with massive dose). GKA is in phase 2 clinical trials, 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. Newly synthesized receptors are packed in vesicles, which transport the receptors to the plasma membranes. During the transportation, they undergo post translational modifications[70]. Upon binding of a ligand to its specific GPCR, it undergoes a conformational change, which is transmitted to the cytoplasmic portion of the protein[71]. This enables coupling with an intracellular heterotrimer G protein (GTP binding protein)[72]. These receptors have diverse role to play. They also have an important role to play in regulation of Islet function. GPCR are also expressed in the pancreatic islet where they regulate glucose level by modulating insulin secretion and various other factors. 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[73,74]. Recently, it has also been proposed that reduced β-cell mass is associated with type 2 diabetes[75,76]. Since glycemic control of type 2 diabetes often deteriorates in spite of aggressive treatment[76], 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 GPCR are involved in the regulation of insulin and glucagon secretion, they serve as potential drug targets. Several approaches have been undertaken to target GPCR for new treatment[77,78]. G-protein-coupled receptors (GPCR) have shown promising result in the treatment of T2D because of their potential involvement in islet function. There are also numerous orphan GPCR whose ligands and effects are not yet known[79]. It is also known that many diseases are linked to GPCR. 

**Islet Gpcr As Potential Drug Targets** 

G protein coupled receptors (GPCR) is the largest class of cell surface receptors. These are also known as metabotropic receptors or 7-transmembrane spanning (heptahelical) receptors. They are membrane receptors that are coupled to intracellular effector systems via a G-protein which consist of three subunits α, β and γ. The GPCR 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. These receptors have a similar topology consisting of a core of 7 transmembrane-spanning α-helices with 3 hydrophilic intracellular and 3 hydrophilic extracellular loops; the N-terminus is located extracellularly, and the C-terminus is located intracellularly. Four different types of G proteins have been identified which are of pharmacological importance Go, Gs, Gi, Gq. Gs and Gi produce, respectively, stimulation and inhibition of enzyme adenyl cyclase. The Gq pathway stimulates PLC-β to produce inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 triggers the release of Ca2+ 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. Newly synthesized receptors are packed in vesicles, which transport the receptors to the plasma membranes. During the transportation, they undergo post translational modifications[70]. Upon binding of a ligand to its specific GPCR, it undergoes a conformational change, which is transmitted to the cytoplasmic portion of the protein[71]. This enables coupling with an intracellular heterotrimer G protein (GTP binding protein)[72]. These receptors have diverse role to play. They also have an important role to play in regulation of Islet function. GPCR are also expressed in the pancreatic islet where they regulate glucose level by modulating insulin secretion and various other factors. 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[73,74]. Recently, it has also been proposed that reduced β-cell mass is associated with type 2 diabetes[75,76]. Since glycemic control of type 2 diabetes often deteriorates in spite of aggressive treatment[76], 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 GPCR are involved in the regulation of insulin and glucagon secretion, they serve as potential drug targets. Several approaches have been undertaken to target GPCR for new treatment[77,78]. G-protein-coupled receptors (GPCR) have shown promising result in the treatment of T2D because of their potential involvement in islet function. There are also numerous orphan GPCR whose ligands and effects are not yet known[79]. It is also known that many diseases are linked to GPCR. 

**GPCR receptors in Glucose and Glucagon regulation** 

Various GPCR receptors are involved in glucose and glucagon regulation. These include the GPCR receptors such as, GIP receptor (GIPR), pituitary adenylate cyclase-activating polypeptide, Adrenergic, Muscarinic, CCK receptors, NPY receptors, Somatostatin receptors, Glucagon, Vasopressin, Cannabinoid Receptors and purinergic receptors. 

**GIP Receptors** 

They have been identified in human pancreatic islets[80]. GIPR are predominantly expressed in β cells[81]. They are linked to Gs protein. GIP increase glucose stimulated insulin secretion[82,83], and inhibits β-cell apoptosis[84]. However, it stimulates glucagon secretion under euglycemic conditions[85]. The role of GIP signaling in glucose homeostasis and insulin secretion has been demonstrated in mice lacking GIPR. These mice exhibit reduced glucose-stimulated insulin secretion after oral administration of glucose, which results in mild glucose intolerance[86]. However, the islet response to...
intraperitoneal glucose was normal, demonstrating that the GIPR 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 [97]. The reason for this has recently been suggested to be secondary to hyperglycemia as demonstrated experimentally both in vivo [108] and in vitro [99]. As GIP effects β-cell function, the GIPR may be a target for treatment. But GIP appears to be insufficient in stimulating insulin secretion in subjects with diabetes [87,90,91].

GLP-1 Receptors
The GLP-1 receptor is expressed in islet β and δ cells. One study demonstrated GLP-1 receptors in rat pancreatic islets α, β and δ cells [92], while others have been unable to detect the receptor in α cells [93]. It is possible that this discrepancy is due to the fact that GLP-1 receptors seem expressed only in a subpopulation of α cells [84]. 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 [89]. The other functions include activation of PKB and increased expression of pancreas duodenal homebox-1 (Pdx1). These two factors have been suggested to be involved in islet proliferation and cytoprotection [96,97,98]. GLP-1 is important in glucose homeostasis and energy metabolism. Studies on mice where the receptors have been inactivated have demonstrated reduced insulin secretion after oral administration of glucose in association with impaired glucose tolerance [69]. 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 [99]. Double incretin receptor knockout (DIRKO) mice have impaired but not completely absent insulin response to oral glucose, showing that also other mechanisms contribute. Interestingly, the DIRKO mice have also impaired insulin secretion to parenterally administered glucose, which shows that the GLP-1 and GIPR are important for a normal glucose competence in the β cells. Two GLP-1 receptor agonists are exendin-4 (exenatide) and liraglutide. Exenatide has been shown to efficiently reduce HbA1c in combination with metformin or sulphonylurea and to reduce body weight. Liraglutide is under clinical trials which also reduces HbA1C in type 2 diabetics.

Neurotransmitter receptors
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 GPCR, stimulating both insulin and glucagon secretion. The sympathetic nerves contain noradrenaline, galanin and neuropeptideY (NPY). Sympathetic nerves activation inhibits glucose-stimulated insulin secretion and stimulates glucagon secretion [100]. 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 [101]. Cholecystokinin (CCK) is another neuropeptide that has been found in islet nerves. Since CCK is a potent stimulator of insulin secretion it is possible that CCK has insulinotropic action through the activation of CCK receptors on the β cells. All these neurotransmitters signal through specific GPCR and regulate insulin secretion through several pathways.

Pituitary adenylate cyclase-activating polypeptide (PACAP) and Vasoactive Intestinal Polypeptide (VIP) Receptors
PACAP and VIP receptors are of 3 different subtypes, PAC1, VPAC1 and VPAC2, and of these, PAC1 and VPAC2 are expressed in the β cells [102]. These receptors are linked to the Gs protein which ultimately results in stimulation of insulin secretion [103]. Disruption of the PAC1 receptor in mice results in impaired insulin secretion after PACAP administration [104]. However, these mice also display reduced glucose-stimulated insulin secretion following both oral and intravenous glucose administration, which suggests that the PAC1 receptor is important for the effect of glucose [104]. Furthermore, VPAC2−/− mice exhibit reduced insulin secretion but maintained glucose tolerance after intravenous administration of glucose, suggesting peripheral effects on insulin sensitivity [105]. PACAP and VIP also stimulate glucagon secretion [103].

Adrenergic receptors
Both β2- and α2-adrenoceptors are expressed in the islets. Noradrenaline has been shown to stimulate insulin and glucagon secretion through the β2-adrenergic receptors [106,107]. At the same time, noradrenaline also interacts with α2-adrenoceptors, which results in the inhibition of insulin secretion and the stimulation of glucagon secretion [107]. Therefore, catecholamines may affect insulin secretion both as stimulators through β2-adrenoceptors and as inhibitors through α2-adrenoceptors. The adrenoceptors are GPCR; β2-adrenoceptors are linked to activation of cAMP, whereas α2-adrenoceptors are linked to inhibition of cAMP production and opening of K+ channels. Three subtypes of the α-adrenoceptors have been described, called α2A-, α2B- and α2C-adrenoceptors. A recent study explored which of those that is of relevance for the inhibition of insulin secretion by using selective knockout mice [108]. It was found that adrenaline did not inhibit insulin secretion in mice with a double knockout of α2A and α2C-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 α2-adrenoceptors mediate the inhibition of insulin secretion by catecholamines. Conversely, transgenic mice with β-cell-specific overexpression of α2A-adrenoceptors displayed reduced glucose-stimulated insulin secretion and impaired glucose tolerance [109], 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.

**CCK receptors and muscarinic receptors**

Both CCK and muscarinic agonists stimulate insulin and glucagon secretion via coupling to Gq. CCK acts locally on CCKA receptors in the gastrointestinal tract to stimulate vagal afferents and may, in its capacity as a neurotransmitter, also act on CCKB receptors in the brain. 5 different muscarinic receptor subtypes exist (M1, M2, M3, M4, M5). Of these receptor subtypes CCKA receptor and the M3 muscarinic receptor are involved in the islet actions. Studies demonstrate that infusion of CCK stimulates insulin secretion in subjects with type 2 diabetes, which would suggest a potential of developing islet specific CCKA receptor agonists in the treatment. The physiological role of the M3 muscarinic receptors was recently explored in a study using β-cell-specific M3 receptor knockout and β-cell-specific M3 overexpression in mice. It was found that mice with M3 muscarinic receptor knockout had reduced insulin secretion and impaired glucose tolerance, whereas M3 muscarinic transgenic mice had increased insulin secretion and glucose tolerance. Therefore, M3 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. M3 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. However, this strategy has serious drawbacks due to general cholinergic effects.

**NPY receptors**

Y1, Y2, Y3, 4, Y5 and Y6 are the different NPY receptors all of which are GPCR. NPY, a neurotransmitter, is found in the autonomic sympathetic nerve terminals in the islets. NPY inhibits insulin secretion. This effect is mediated by the NPY Y1 receptors through inhibition of adenylate cyclase activity, presumably by Gi. Islet β cells express the Y1 receptors. NPY also promotes β-cell replication. But even in absence of NPY Y1 receptor (as is the case of NPY Y1 receptor gene knockout mice), glucose-stimulated insulin secretion is normal. Thus the role of these receptors in glucose utilization is doubtful. Due to its inhibitory action on insulin secretion, Y1 receptors are not an appropriate target for treatment of diabetes.

**Glucagon receptors**

The glucagon receptor is a GPCR. Glucagon has a crucial role in maintaining circulating glucose levels mainly through its stimulation of hepatic glucose production. Glucagon receptors (Gcgr) are expressed on pancreatic β cells, and glucagon stimulates insulin release. Binding of glucagon results in the activation of the Gsα and Gq proteins. Islets rich in glucagon are more sensitive to glucose, thus secreting more insulin than islets containing fewer α cells. This evidence supports the idea that glucagon is important for the insulin response to glucose. Mice lacking glucagon receptors display low circulating glucose levels and show improved glucose tolerance. Glucagon levels are often elevated in type 2 diabetes. So this hyperglucagonemia may contribute in maintaining hyperglycemia. Particularly when insulin levels are low or during insulin resistance, hyperglucagonemia results in increased hepatic glucose production. This implies that if the glucagon signal is inhibited, type 2 diabetes can be controlled due to reduced glycemia, improved islet function as well as improved insulin sensitivity. But it should be noted that glucagon receptors only outside islets should be inhibited. Because inhibiting glucagon receptors within islets would impair insulin release as well as two these hormones are mutually controlled.

**Somatostatin receptors**

sstr1, sstr2b, sstr3, sstr4 and sstr5 are the five types of somatostatin receptors found in humans. All are GPCR and are expressed in β cells. The sstr2 is the receptor subtype that mediates the inhibition of insulin and glucagon secretion by somatostatin. This receptor subtype couples to Gi/Go proteins, which results in inhibition of adenylate cyclase activity. Somatostatin inhibits insulin secretion. So it has not been used in the treatment of diabetes. But it can be used in the treatment of exaggerated insulin secretion in insulinomas and other types of hyperinsulinemia. The somatostatin analogue octreotide has given favourable results in this aspect. GPR54 couples to Gq and the PLC pathway. Kisspeptin ia a ligand to GPR54. The gene from which kisspeptins are transcribed, KISS1, is a tumoursuppressor gene in breast cancer cells. But products of this gene can also act as energy sensors. Kisspeptin is one of them. GPR54 is expressed in hypothalamic neurons as well as in the pancreas and the placenta. 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. Furthermore, the addition of kisspeptin to isolated islets potentiates glucose-stimulated insulin secretion, while the peptide has no effect on glucagon secretion. But the extent of involvement of this receptor in glucose metabolism is yet to be known.

**Cannabinoid receptors**

CB1 receptors (and also CB2 receptors) were found in islets. Their activation inhibited insulin secretion through a Ca2+-dependent mechanism. Cannabinoid receptors are GPCR, which are expressed mainly in the brain. The CB1 receptor binds Δ9-tetrahydrocannabinol. The cannabinoid system has been suggested to be involved in the regulation of food intake. This can be deduced from the fact that antagonism of the CB1 receptor and deletion of CB1 receptors reduce food intake and body weight. CB1 receptor activation by anandamide induces glucose intolerance in rats. The effect is exactly opposite in case of CB1 receptor antagonist. Hence, CB1 receptors may be targets also for affecting islet function in diabetes.
Vasopressin stimulates the secretion of both insulin and glucagon. There are four types of GPCR which have connection to the action of vasopressin. They are V1A, V1B, V2 and OT (oxytocin) receptors.[122] The V1A vasopressin receptor has received most of the attention. It couples to Gq and activates PLC. The receptor subtype responsible for these islet actions is V1B as confirmed by recent studies. (Mice with genetic deletion of V1B receptors display lost insulinotropic action of vasopressin). Therefore, vasopressin-induced islet actions seem mediated by the V1B receptor.

**Purinergic receptors**

Two types of purinergic receptors are expressed on islets: P1 (activation inhibits insulin secretion through inhibition of adenylyl cyclas) and P2 (receptor activation stimulates insulin secretion through a Ca2+-dependent mechanism).[123] It is the P2Y1 receptor subtype of the P2 receptor complex that is expressed in islets. Studies in rats have shown that a selective P2Y receptor agonist stimulates insulin secretion. This makes P2Y purinergic receptor as a good target for treatment of diabetes. P2Y receptors are now tested as a potential drug target for diabetes. Some of the P2Y receptor agonists have shown promising effects in experimental studies. Many GPCR 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. The GPCR have attracted considerable attention due to their potential as targets in novel drug development and the orphan GPCR where the ligands have still not been identified are of particular interest. The GLP-1 receptor upon activation has multiple positive effects. It stimulates insulin secretion and inhibits glucagon secretion. Thus, it is the most promising novel drug target. Both GPCR with known ligands as well as the orphan GPCR need to be studied with regard to tissue localization and ligand specificity. Most promising are M3 muscarinic receptors and P2Y receptors.

**CONCLUSION**

The recent development in the DPP IV inhibitors, Glucokinase activators and GPCR receptors has proven to be a potential targets for the treatment of T2D. The DPP IV inhibitors like Sitagliptin have proven to be promising given along with the present drugs. The metformin have significant clinical uses and less toxic effect. The glucokinase activators have also proved to be beneficial in treating T2D. The drugs that are glucokinase activators are presently under preclinical or clinical trials. Drugs coded as TTP399 and ARRY403 are under preclinical trials. AZD6370 is under Phase II clinical trials. But they have shown promising results. GPCR is a potential target for T2D treatment. The various types of receptors that regulate the level of glucose and glucagon are GIP receptors, GLP-1 receptors, CCK receptors, muscarinic receptors NPY receptors, somatostatin receptors and glucagons receptors. These have proved to be useful for T2D treatment. These developments can be developed as new therapy for proper T2D treatment. The drugs in these categories have shown better results. These drugs have fewer side effects and mostly overcome the problems faced in the present drugs for diabetes.

**REFERENCES**

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