



International Journal of Pharmacology

ISSN 1811-7775

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Molecular Targets in the Development of Antidiabetic Drugs

¹Adel S. Al-Zubairi and ²Eltayeb Elamin M. Eid

¹Department of Biochemistry and Molecular Biology,
Faculty of Medicine and Health Sciences, University of Sanaa, Sanaa, Yemen

²Laboratory of Cancer Research UPM-MAKNA, Institute of Bioscience,
University of Putra Malaysia, Serdang, SDE, Malaysia

Abstract: Type 2 diabetes mellitus (T2DM) is a worldwide public health problem. The fact that the existing treatments have limitations either because of their side effects as hypoglycaemia and weight gain or their other complications necessitate the need for development of new therapies for glycemic control. The therapeutic approaches represented by the incretin-based therapies, namely the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon like peptide-1 (GLP-1) analogues/mimetics, offer a new therapeutic means for treatment of T2DM, in addition to other several even newer therapies in development. A great attention has been focused by many researchers on a number of potential molecular targets in fat cells or adipocytes, as the adipokines. In this article we will review the development of the possible molecular targets for the currently available antidiabetic agents with particular emphasis on incretin-based therapeutic targets as well as molecular targets in adipocytes and other future therapies.

Key words: Adipokines, incretins, SGLT, insulin resistance, PTEN

INTRODUCTION

In order to minimizing the adverse effects of many currently used drugs, researchers are continuously searching for new drug leads having more potency with less complications. In drug discovery and development, early-phase studies usually designed to evaluate safety, tolerability and pharmacokinetics of new drug leads (Abdul *et al.*, 2008a, b, 2009; Abdel-Wahab *et al.*, 2009; Al-Zubairi *et al.*, 2010a, b) when the target of the drug lead is not well defined. Pharmaceutical agents generally exert their therapeutic effect by binding to and regulating the activity of a particular protein or nucleic acid target. Modern drug discovery has been primarily based on the search of leads directed against a preselected target and the subsequent testing of the derived drug candidates. Continuous efforts and interest have been directed at the discovery of new targets, as well as more-extensive exploration of the targets of successful drugs (Drews, 1997; Ohlstein *et al.*, 2000). In general, the aim of targeted therapies is to increase the efficacy and reduce the toxicity of drugs.

Diabetes mellitus is a common, serious metabolic disorder characterized by a defect in insulin production and/or in insulin action on peripheral tissues leading to

metabolic abnormalities and hyperglycemia (Shalam *et al.*, 2006; American Diabetes Association, 2007; Kawahito *et al.*, 2009). The disease can be divided into two major classes: insulin-dependent diabetes mellitus, also known as type 1 diabetes and non-insulin-dependent diabetes mellitus, also known as type-2 diabetes (World Health Organization, 1985). Type 1 results from insulin deficiency caused by cell-mediated autoimmune destruction of pancreatic β -cells and generally developed in young (Bach, 1995). Based on World Health Organization and American Diabetes Association data, studies in several countries have estimated that there will be 285 million people with diabetes worldwide in 2010 (Shaw *et al.*, 2010). About 90% of diabetes cases are type 2 diabetes mellitus, which is characterized by peripheral insulin resistance and insulin deficiency and generally develops in adults (Yki-Jarvinen, 1994). However type 2 can also be developed at a younger age, as seen in the maturity onset diabetes of the young (MODY).

Type 2 diabetes mellitus is currently thought to be influenced by more than a single gene or environmental factors resulting in development of insulin resistance and β cell dysfunction (Taylor, 1999; Saltiel and Kahn, 2001; Ghosh and Schork, 1996; Stumvoll *et al.*, 2005). The contribution of genetic and environmental factors to the

development of type 2 diabetes differs among individuals. Patients generally have two common metabolic abnormalities: insulin resistance and defects in glucose-stimulated insulin secretion, which lead to the disease (Saad *et al.*, 1991; DeFronzo *et al.*, 1992; Lillioja *et al.*, 1993). Genetic factors play an important role in the pathogenesis of type 2 diabetes mellitus. This is clear from the familial aggregation and the high concordance rate for the disease (60-100%) in identical twins (O'Rahilly *et al.*, 1988; Jun *et al.*, 1999). As well as the environmental factors such as obesity, physical activity and diet that play a strong role in the development of the disease (Helmrich *et al.*, 1991). The adipose tissue seems to play an important role in the pathogenesis of type 2 diabetes. Hence the obesity is the key risk factor for type 2 diabetes at a young age (Kiess *et al.*, 2001, 2003; Strauss and Pollack, 2001; Palmert *et al.*, 2002; Jones *et al.*, 2002). A genetic predisposition is generally believed to be required for the development of type 2 diabetes.

Pathophysiology of type 2 diabetes mellitus: The causes of type 2 diabetes are multifactorial including of both genetic (Gerich, 1998) and environmental factors that with the increasing prevalence of obesity, the prevalence of type 2 diabetes is reaching epidemic proportions (Scheen, 2001). Interactions of these factors affect beta-cell function and tissue insulin sensitivity. The progressive development of Type 2 diabetes mellitus start with the predisposing genetic factors starting with disturbance in glucose homeostasis in which initially individuals are at risk for type 2 diabetes because of genetic polymorphisms. Later on, as a result of a genetic predisposition and lifestyle, reduced insulin sensitivity probably emerges, which are initially compensated for by an increase in β cells function, so that glucose tolerance remains normal (Hales, 1994), but later both the β cells and insulin sensitivity, deteriorate leading to impaired glucose tolerance. Finally, as a result of further deterioration of β cells function, both fasting and postprandial blood glucose levels reach clearly diabetic levels and the patients become symptomatic. Thus, the development of new classes of drugs for treatment of diabetes mellitus needs to explore new targets to supplement older therapies, including lifestyle-directed interventions, insulin, sulfonylureas and metformin.

Antidiabetic drugs: Due to the absence of hormone synthesis, Type 1 diabetes mellitus requires insulin therapy from the beginning. While, type 2 diabetes can be managed by various means of treatments including insulin administration, stimulation of insulin release from the beta

cells by sulfonylureas and metiglinides, increasing peripheral tissue utilization of glucose with receptor sensitizers such as the thiazolidinediones, decreasing hepatic glucose production (the biguanides) and decreasing utilization of ingested carbohydrates (α -glycosidase inhibitors such as acarbose and miglitol). The current anti-diabetic drugs lower blood glucose levels by one or more of the above listed mechanisms (Nathan, 2002; Chan and Abrahamson, 2003; Zangeneh *et al.*, 2003). The classification of antidiabetic agents has been reviewed by Mehanna (2005) who categorized them into insulin pharmaceutical preparations and oral antidiabetic drugs. Insulin preparations were classified based on the onset and duration of action into rapid, intermediate and long-acting preparations. Meanwhile, oral antidiabetic agents were classified into five classes: sulfonylureas, non-sulfonylurea secretagogues (the thiazolidinediones), biguanides, insulin receptors sensitizers and α -glucosidase inhibitors (Tahrani *et al.*, 2010).

Molecular targets: The main molecular targets for drugs are proteins (mainly enzymes, receptors and transport proteins) and nucleic acids (DNA and RNA). These molecular targets are undergoing a selective interaction with chemicals administered to treat or diagnose a disease. They are human genome-derived proteins, or belong to pathogenic organisms. A limited set of drugs act through physicochemical mechanisms, or have unknown mechanisms of action.

Analysis of the human genome in 2002 led to the estimation of 6000-8000 targets of pharmacological interest. Only a small part of these targets relates to approved drugs. In Drews and Ryser estimated the number of molecular targets by all marketed drug substances to be only 483 (Drews and Ryser, 1997). Hopkins and Groom estimated that drugs acted primarily through only 120 underlying molecular targets (Hopkins and Groom, 2002) while in 2003, Golden proposed that all the approved drugs acted through 273 proteins (Golden, 2003). Zheng *et al.* (2006) disclosed 268 successful targets in the current version of the therapeutic Targets Database, Zheng *et al.* (2006) and Imming *et al.* (2006) catalogued 218 molecular targets for approved drugs. A consensus number of 324 drug targets for all classes of approved therapeutic drugs were proposed by Overington *et al.* (2006). Of these, 266 are human genome-derived proteins and 58 are bacterial, viral, fungal or other pathogenic organism targets.

Generally, old therapies that target pancreatic beta cells and stimulate insulin secretion, targeting the three major defects associated with type 2 diabetes; defective insulin secretion, increased hepatic glucose output and

insulin resistance. However, drugs used for these targets are almost had many problems in long term use. Thus scientists are looking for new approaches for management of diabetes mellitus. Recently, researchers plans include bridging the gap between understanding the role of lipids and exploring signal transduction pathways mainly in diabetes. They need to investigate how lipids, carbohydrates and kinases interact in normal and abnormal conditions as well as establishing relationships to diets, diseases and prevention. These specific interactions between proteins and lipids can be studied at several levels: at molecular level by investigating the possible structural interactions, biochemically by analyzing membrane microdomains in normal and abnormal conditions and finally genetically by exploring gene expression.

Recent drug targets for diabetes mellitus: The investigation of selective inhibition or activation of oncogenes by lipids through the analysis of gene expression modulation by specific nutrients, or via the molecular study of the occurrence of such interactions, may lead to the development of new areas of diabetes treatment, e.g. intestinal endocrine cells and adipocytes.

PTEN: PTEN is a dual-specificity protein phosphatase involved in signal transduction and tumour suppression. PTEN has phosphoinositide 3-phosphatase activity and is therefore capable of suppressing PI3K signalling by dephosphorylating PIP3 (Maehama and Dixon, 1998; Lee *et al.*, 1999). Because many of the metabolic effect of insulin are mediated through the activation of PI3K and the subsequent raise in intracellular PIP3 concentration, of this pathway, may enhance insulin signaling through the feedback inhibition as a pnegative regulator. PTEN inhibition lead to the translocation of GLUT4 to the plasma membrane where its exocytosis participates to increase glucose uptake (Nakashima *et al.*, 2000; Thong *et al.*, 2005), as well as overexpression *in vitro* inhibits glucose uptake and GLUT4 transport in 3T3LI cells. These results suggest that PTEN may modulate insulin signaling *in vivo*. Therefore, PTEN represent a good target for the reduction of blood glucose level by inhibiting its expression, as it play a role in glucose metabolism *in vivo* by negatively regulating insulin signalling. Therefore, depending on where the defect in the insulin signalling cascade occurs, PTEN targeting might help to overcome insulin resistance leading to reduction of blood glucose levels.

Adipocytes: Adipocytes have a considerable effect on glucose homeostasis mediated by endocrine and

non-endocrine mechanisms. The endocrine participation of adipocytes is mainly through the synthesis and release of peptide hormones, the so-called adipokines (adipocyte-derived proteins with antidiabetic action include leptin, adiponectin, omentin and visfatin) (Berg *et al.*, 2002; Fukuhara *et al.*, 2005; Yang *et al.*, 2005, 2006). In addition to its well characterized role in energy balance, leptin reverses hyperglycemia by improving insulin sensitivity in muscles and the liver. Intracellular lipids may contribute to insulin resistance, this occurs most likely by reducing intracellular lipid levels through a combination of direct activation of AMP-Activated Protein Kinase (AMPK) and indirect actions mediated through central neural pathways (Minokoshi *et al.*, 2002). Other factors tend to raise blood glucose, including resistin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and retinol-binding protein 4 (RBP4). TNF- α is produced in macrophages and reduces insulin action (Hotamisligil, 1999).

Adipocytes also release non-esterified fatty acids (NEFAs) into the circulation, which act as one of the adipocyte-derived secreted non-endocrine product. However, insulin resistance is also associated with lipolysis and NEFA release into the circulation due to reduced muscles and adipocytes glucose uptake and promoted hepatic release. Transiently elevated NEFAs (such as occur after a meal) tend to enhance insulin secretion, whereas chronic elevations in NEFAs (such as occur in insulin resistance) (Eldor and Raz, 2006) tend to reduce insulin secretion which may involve lipotoxicity induced apoptosis of islet cells (Lowell and Shulman, 2005). It has been suggested that insulin resistance in adipocytes is the first metabolic manifestation leading to type 2 diabetes mellitus (Bergman, 1997). Insulin resistance in adipocytes, paradoxically a condition in obesity in which insulin cannot promote a normal fat storage, resulting in excess circulating fatty acids that in turn, promote insulin resistance in muscle and consequently type 2 diabetes mellitus (Pilch and Berghem, 2006). Thus pharmacological targeting of fat cells to correct this abnormality seems to be a very promising strategy. Accordingly, there are three independent targets in adipocytes that may suitable for the treatment of diabetes; adipokines, modulator of hormonal sensitivity and enzymes involved in fat storage.

Adipokines: These are cytokines, (they are proteins, peptides or polypeptides act as signaling molecules used extensively in cells communication) secreted by adipose tissue, such as leptin, adiponectin and resistin and they considered as potential targets for the treatment of diabetes mellitus.

Leptin: Leptin is a protein hormone with important effects in regulating body weight and metabolism, expressed predominantly by adipocytes (Zhang *et al.*, 1994) and the lack of functional leptin or leptin receptor causes massive obesity and diabetes in humans (Friedman, 1998). It has an important role in the regulation of food intake and energy expenditure and it is a major contributor to metabolic and neuroendocrine function both in animals and humans (Himms-Hagen, 1999). Its principal target is the central nervous system, although peripheral actions have been reported (Bjorbaek and Kahn, 2004). In humans and rodents that have molecular defects in leptin expression, its administration represent an effective therapy for their obesity (Farooqi *et al.*, 2002) however, most obese patients have high levels of circulating leptin in their bodies and are resistant to the actions of this adipokine even when exogenously administered (Heymsfield *et al.*, 1999). Increased plasma leptin levels act to increase peripheral insulin sensitivity. In vivo observations showed that both peripheral and central administration of leptin increased skeletal muscle glucose uptake (Kamohara *et al.*, 1997; Wang *et al.*, 1999) and oxidation (Ceddia *et al.*, 1999).

Adiponectin: Adiponectin is an adipocyte-derived hormone discovered independently by four groups (Pilch and Bergenheim, 2006). It suppresses hepatic glucose production (Berg *et al.*, 2001) and also stimulates oxidation of fatty acids primarily in skeletal muscle and the liver (Yamauchi *et al.*, 2001), thereby preventing the accumulation of lipids in insulin target tissues. Adiponectin has become the most widely used name for this adipokine. Circulating adiponectin levels correlate with insulin sensitivity in humans; interestingly, injection of adiponectin in mice has been shown to induce weight loss (Berg *et al.*, 2001). Serum adiponectin levels are reported to be decreased in obesity (Arita *et al.*, 1999). Moreover, it has been demonstrated that the decreased expression levels of adiponectin coincided with insulin resistance in murine models of altered insulin sensitivity (Yamauchi *et al.*, 2001).

PPAR_γ: Peroxisome Proliferator-Activated Receptor (PPAR) are a family of three (α , β/δ and γ) nuclear receptors that affect the transcription and expression level of numerous target genes in adipocytes and other tissue/cells (Feige *et al.*, 2006). They have emerged as central regulators of lipid homeostasis and molecular targets for drugs to treat hyper-triglyceridaemia and type 2 diabetes mellitus and they have been implicated in variety of pathological states (Glass, 2006; Michalik and Wahli, 2006; Semple *et al.*, 2006). PPARs are activated by

a wide range of naturally occurring or metabolised FFA and eicosanoid-FFA derivatives and TZDs (thiazolidinediones). By lowering circulating lipids, PPARs oppose lipid-induced insulin resistance (Evans *et al.*, 2005; Straus and Glass, 2007). PPAR_γ is an extensively studied member of PPAR family because its agonist has been used clinically and commercially for diabetes therapy for approximately 10 years. It was reported to play a critical role as metabolic regulator through stimulating insulin sensitivity, glucose-lowering and lipid uptake and storage in peripheral organs such as skeletal muscle, liver and adipose tissue (Lehrke and Lazar, 2005). The first insulin sensitizer and PPAR_γ agonist used was troglitazone (Rezulin), which was taken off from the market in 2000 because of liver toxicity, but now Rosiglitazone and Pioglitazone which are used for this purpose and considered to be the most potent and selective PPAR_γ agonists (Yki-Jarvinen, 2004; Henke, 2004). Increasing evidence suggests that natural and pharmacological PPAR_γ ligands induce rapid effects in different cell systems expressing high levels of PPAR_γ (Luconi *et al.*, 2010).

Enzymes of fat metabolism: Storage of even modest caloric surplus in tissues other than white adipose tissues leads to insulin resistance and the development of diabetes (Unger, 2002). The precise identity of the lipid factor responsible development of insulin resistance is not known, although free fatty acids, long-chain fatty acyl-CoAs, 1,2 diacylglycerol and ceramide are probable suspects (McGarry, 2002). An ideal approach to treat obesity and diabetes would be to decrease fat storage and enhance its oxidation. A very promising approach is to use a classic type of drug such as enzyme inhibitors, like receptor agonists and antagonists. Thus, this approach will be promising in the treatment of type 2 diabetes mellitus.

SCD1: Stearoyl-CoA desaturase-1 (SCD1) is a central enzyme responsible for the synthesis of monounsaturated fatty acids-mainly oleate (C18:1) that is a major component of tissue lipids, triglyceride and membrane lipids synthesis and it is highly expressed in adipocytes as well as in liver (Ntambi *et al.*, 1988). SCD1 has been shown to be an important control point of lipogenesis (Ntambi and Miyazaki, 2004; Dobrzyn and Ntambi, 2004). Furthermore, SCD1 has been found to be a major peripheral target gene of leptin-mediated signalling events (Cohen *et al.*, 2002). One of the mechanisms of SCD1 is via increased activation of AMP-Activated Protein Kinase (AMPK) (Dobrzyn *et al.*, 2004). SCD1 deficiency increases the rate of fatty acid β -oxidation through activation of the AMPK

pathway and by upregulating genes of fatty acid oxidation in skeletal muscle (Dobrzyn *et al.*, 2005). However, partial inhibition of SCD1 by appropriate small molecule might have beneficial metabolic actions (Cohen and Friedman, 2004). Therefore, SCD might be a potential therapeutic target in the treatment of the metabolic syndrome and diabetes and indication that the inhibition of this enzyme is both safe and efficacious.

DGAT1: Accumulation of triglycerides leads to the obesity and associated with insulin-resistance, so inhibition of triglycerides synthesis represents a potential therapeutic strategy for human obesity and type 2 diabetes. The microsomal enzyme, acyl-CoA:diacylglycerol acyltransferase 1 (DGAT1) catalyzes the final and committed step in the biosynthesis of triglycerides by covalently joining a long chain fatty acyl-CoA to diacylglycerol (Farese *et al.*, 2000). Partial DGAT1 deficiency in Knockout mice was observed to have an increase insulin sensitivity (Chen *et al.*, 2002; Chen and Farese, 2005) that has been attributed to increased insulin-stimulated glucose transport in the skeletal muscle and White Adipose Tissue (WAT) (Chen *et al.*, 2004). These observations very recently have been confirmed in Zucker fatty rat and the hyperlipidemic hamster (King *et al.*, 2009). Therefore, partial inhibition of this enzyme might also have a promising target for the treatment of diabetes mellitus.

11 β -HSD1: 11 β -Hydroxysteroid dehydrogenase (Type 1) (11 β -HSD1) catalyzes the conversion of inactive cortisone to active cortisol in the liver and adipose tissue. High levels of cortisol are well known to cause insulin resistance (Friedman *et al.*, 1996) in fact, increase expression of 11 β -HSD1 adipocytes has been reported in acquired obesity and diabetes. Pharmacological inhibition or transgenic disruption of 11 β -HSD1 attenuates glucocorticoid action and increases insulin sensitivity (Walker *et al.*, 1995). Mice lacking functional of 11 β -HSD gene have been shown to be resistant to developing diabetes when put in a high fat-diet (Morton *et al.*, 2004). 11 β -HSD1 inhibition may also be beneficial in the pancreatic β -cells, where regeneration of glucocorticoid by 11 β -HSD1 may inhibit insulin secretion (Davani *et al.*, 2000) as these effects also have been predicted from in vitro studies (Handoko *et al.*, 2000). Therefore, these findings have promoted interest in inhibition of 11 β -HSD1 as a drug target for treatment of diabetes as currently being developed.

β_3 -adrenergic receptors: β_3 -adrenergic receptors (β_3 -AR) are expressed mostly in fat tissues (Krief *et al.*, 1993; Arch

and Kaumann, 1993; Berkowitz *et al.*, 1995; Collins *et al.*, 2004) and plays a significant role in controlling energy expenditure through the regulation of lipolysis and thermogenesis in brown adipose tissue (Umekawa *et al.*, 1997). Their activation with selective agonists stimulates lipolysis and release of fatty acids in white adipose tissue and also activation of thermogenesis in brown adipose tissue (Arbeeny *et al.*, 1995; Liu and Stock, 1995; Nagase *et al.*, 1996; Grujic *et al.*, 1997). Reduction of β_3 -AR number in adipose tissue of obese mice and Trp64Arg missense mutation of β_3 -AR in obese humans both indicate a possible role of β_3 -AR in obesity-related insulin resistance (Collins *et al.*, 1994; Hoffstedt *et al.*, 1999; Umekawa *et al.*, 1999). In addition, obese rats treated with β_3 -AR agonists demonstrated an improvement of insulin sensitivity in adipose tissue as well as in skeletal muscle (Moreno-Aliaga *et al.*, 2002). However, the actual physiological role of β_3 -AR in humans is not clear due to the lack of a highly selective β_3 -AR agonist despite continuous trials over the past 20 years. Chronic administration of β_3 -AR agonists has demonstrated antidiabetic and antiobesity effects in obese and diabetic rodent models (De Souza and Burkey, 2001; Arch, 2002). Possible antidiabetic effects of β_3 -AR agonists have been suggested by the observation of improved insulin-stimulated glucose disposal with enhanced insulin action in adipose tissues but with unchanged circulating glucose, insulin and lipid levels in normal Sprague-Dawley rats after chronic activation of β_3 -AR (Kiess *et al.*, 2001).

Promising drugs targeting type 2 diabetes: These are drugs recently developed for management of type 2 diabetes mellitus, which were showed an excellent supplement for the old classes. GLP-1 and GIP are the prominent incretin hormones that exert well characterised insulin releasing effects (Green *et al.*, 2004; Drucker and Nauck, 2006; Green and Flatt, 2007; Baggio and Drucker, 2007) and their inhibitor dipeptidyl peptidase 4 (DPP 4) which is largely responsible for their degradation and inactivation *in vivo* (Deacon *et al.*, 2002). The increased understanding of biology and metabolism of incretins hastened the development and use of incretin analogues/mimetics/agonists (which exogenously activate incretin receptors) and DPP 4 inhibitors (which enhance endogenous incretin activity) (Deacon, 2004; Green *et al.*, 2006a; Flatt *et al.*, 2008).

Glucose-Dependent Insulinotropic Peptide (GIP): GIP is secreted in a single bioactive form from the K-cells in the duodenum and jejunum in response to the ingestion of carbohydrates and/or lipids (Fehmann *et al.*, 1995;

Baggio and Drucker, 2007; Gautier *et al.*, 2008). GIP reported to stimulates glucose-dependent insulin secretion in humans (Baggio and Drucker, 2007; Gautier *et al.*, 2008). In addition, it plays a role in fat metabolism in the adipocytes and has a proliferative effect on the β -cells (Yip and Wolfe, 2000; Trumper *et al.*, 2001; Gautier *et al.*, 2008).

Glucagon-like peptide-1 analogues (GLP-1): GLP-1 is one of the incretin hormones, cleaved from pro-glucagon and secreted from the L-cells in the distal ileum and colon (Baggio and Drucker, 2007; Gautier *et al.*, 2008). GLP-1 and GIP contribute and potentiate glucose-dependant insulin secretion in an additive manner but GLP-1 appears to be responsible for the majority of the incretin effects on the β -cell (Baggio and Drucker, 2007). These are new class of drugs for treatment of type 2 diabetes. One of their advantages is that they have a lower risk of causing hypoglycemia. With GLP-1, glucose stop going down when they reach a normal range, e.g., Exenatide. Administration of GLP-1 agonists inhibits glucagon secretion, lowers food intake and reduces body weight in diabetic animals and humans (Green *et al.*, 2006b).

Dipeptidyl Peptidase 4 inhibitors (DPP 4 inhibitors): DPP 4 is responsible on the inactivation of incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) (Baggio and Drucker, 2007), which are normally released in the digestive tract in response to food and mediate glucose-dependent insulin secretion (Deacon *et al.*, 2002). DPP-4 is widely expressed in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine and lymphocytes (Gautier *et al.*, 2008). GLP-1 stimulates glucose -dependent insulin release from the pancreatic islets. Insulin secretion can be enhanced indirectly with DPP 4 inhibitor drugs (gliptins) which minimise degradation of endogenous incretins and result in raised circulating concentrations of the biologically intact forms of GLP-1 and GIP, examples of these are Sitagliptin, Alogliptin and Saxagliptin. Incretins have been suggested to be inactivated immediately following secretion into the blood and this is attributed to their short half life (Deacon *et al.*, 1995; Mentlein, 1999; Baggio and Drucker, 2007; Gautier *et al.*, 2008).

Sodium-dependent glucose cotransporters (SGLT-2): Sodium dependent glucose cotransporters (SGLT) are a family of glucose transporters found in the intestinal mucosa of the small intestine (SGLT1) and the proximal tubule of the nephron (SGLT2 and SGLT1) (Wright, 2001). They contribute to renal glucose reabsorption and

responsible for about 90% of glucose reabsorption. SGLT2 inhibitors promote glycosuria by blocking the reabsorption of glucose in the proximal tubule of the kidney. Selective inhibition of SGLT2 in the proximal tubule increases urinary glucose excretion, but crucially these drugs only appear to have this effect in states of hyperglycaemia thereby reducing plasma glucose levels (Katsuno *et al.*, 2007), which may present a novel therapeutic target for the control of hyperglycemia. Therefore, SGLT represent an excellent target for reduction of hyperglycemia preventing the adverse complications of glucose toxicity observed in diabetes. Sergliflozin (GlaxoSmithKline), Dapagliflozin (Bristol-Myers Squibb and Astra Zeneca) and some of the thioglycosides (Castaneda *et al.*, 2007) are currently under development from this class of drugs.

Glucokinase activators: Glucokinase (GK) is a glucose-sensing enzyme found in the liver and pancreas (Leighton *et al.*, 2005; Matschinsky *et al.*, 2006; Matschinsky, 2009) known to phosphorylate D-glucose. Defects in this enzyme cause disease in humans, such as Maturity-Onset Diabetes of the Young type 2. Activation of this enzyme promotes hepatic glucose uptake and pancreatic insulin secretion and, therefore, is an ideal target for diabetic therapy (Leighton *et al.*, 2005). Agents directed at selectively activating liver glucokinase are currently in development. These should produce only glucose-dependent effects and reduce the potential for hypoglycaemia (Fyfe *et al.*, 2007). Several GKAs have been described during the past years. These compounds (GKA1, GKA2, RO-28-1675 and compound A) directly activate GK (Grimsby *et al.*, 2003; Kamata *et al.*, 2004). Activators of GK offer a potential therapeutic that could be a novel approach to decrease hyperglycaemia in people with diabetes.

CONCLUSION

The development in the understanding of type 2 diabetes mellitus pathophysiology at molecular level increases the number of antidiabetic drugs discovered. The demand to avoid the complications of the old therapeutic agents and to improve the recently discovered drugs enriched the area of antidiabetic drug discovery with the most advanced and less adverse effects small molecular weight drugs. Among the recent antidiabetic therapies are the incretin-based therapies which are the latest marketed development in the field. Incretins are effective in improving glycemic control with low risk of hypoglycaemia. The impact of newer therapies associated with better concordance rates due to improved tolerability

and lower toxicity compared with more traditional agents needs to be fully tested.

ACKNOWLEDGMENT

This study is the outcome of an in-house study and has not been supported financially.

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