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CURRENT ANTIDIABETIC DRUGS AND STRATEGIES FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

A constant increase in the features of metabolic syndrome leading to serious complications including neuropathy, retinopathy and nephropathy has resulted in worldwide epidemic of Type 2 diabetes mellitus or insulin resistance. Most of the available antidiabetic drugs were developed in the absence of defined molecular targets or a clear understanding of disease pathogenesis. Moreover, the available drugs suffer from one or the other side effects. Emerging knowledge of key physiologic mechanisms related to probable causes of hepatic and muscle insulin resistance on glucose metabolism has led to a number of new emerging molecular drug targets. Type 2 diabetes mellitus is a major contributor of deaths in India and worldwide, there is a urgent need to develop new drugs that will be helpful to diminish the overall diabetic load of world population. The present review provides the description of existing antidiabetic drugs and their respective molecular targets. There is a information regarding the antidiabetic targets that include receptors and enzymes that enhance glucose-stimulated insulin secretion, suppress hepatic glucose production, increase skeletal muscle glucose transport and utilization, increase insulin sensitivity and intracellular insulin signaling with reduction in circulating and intracellular lipids. It also emphasizes on the need for developing novel antidiabetic drugs having lower side effects and more efficacy.

KEYWORDS: antidiabetic drugs, targets, type 2 diabetes mellitus, etc.

INTRODUCTION

Diabetes mellitus is now defined as an abnormal state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin.[1] Diabetes mellitus is an epidemic in the world. According to the International Diabetes Federation's 2013 statistics, 382 million people worldwide are diabetic and the diabetic population is estimated to increase to 592 million by 2035.[2,3] The primary symptoms of diabetes mellitus includes elevated fasting and post-prandial blood glucose levels. The continuation of this imbalanced homeostasis does not return to normalcy and leads to hyperglycemia that in due course of time turns into diabetes mellitus.[4]

Classification of Diabetes mellitus

This disease is broadly categorized into two main types i.e. Type-1 (Insulin dependent diabetes mellitus), Type-2 (Non-insulin dependent diabetes mellitus). Gestational diabetes (It is a temporary and appears during pregnancy usually develops during pregnancy. Other form of diabetes occurs due to viral infections as mentioned in Fig 1. After delivery, blood sugar levels generally return to normal) and other specific types (Pancreatic endocrinopathy. Indigenous infections like rubella and cytomegalovirus induced by drugs or chemicals. Other genetic indisposition).[5]

Type-1 diabetes represents a heterogeneous and polygenic disorder caused due to autoimmune destruction of pancreatic beta cells resulting in reduced insulin secretion.[6] Type 1 diabetes mellitus accounts for 5 to 10% of all diabetic cases. Type 2 diabetes mellitus (T2DM) occurs due to abnormality in insulin function resulting into obstructions in insulin signaling pathway.

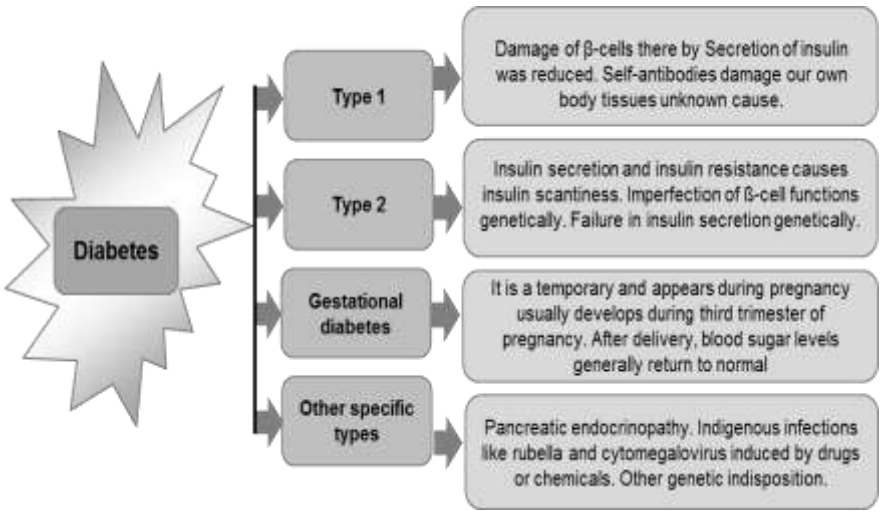

Figure 1: **Types and Symptoms of diabetes mellitus.**

Type 2 diabetes mellitus constitutes defects responsible for insulin resistance in the cells, resulting in numerous complications at later stages caused mainly due to disturbances in the functioning of proteins involved in insulin signal transduction pathway.[7]

Diagnosis of Diabetes mellitus

(1) Diagnostic criteria: Pre-diabetes includes the people with impaired glucose tolerance (IGT, plasma glucose after glucose loading 75g-OGTT is less than 11.1 mmol/L but not less than 7.8 mmol/L or impaired fasting glucose (IFG, fasting plasma glucose is > 5.6 mmol/L but < 7.0 mmol/L), is believed to confer a high risk of developing T2D.[8] So several population-based studies in individuals of pre-diabetes were performed.[9,10,11,12,13,14] The normal range of blood glucose exists between (80-120) mg/dl. An individual is said to be diabetic if the blood glucose level after 12 hours of fasting exceeds 120mg/dl and postprandial blood glucose exceeds 180 mg/dl.

Table 1: Data of plasma glucose (5).

Type	Diagnosis	Plasma Glucose (mmol/L)
Normal	Fasting and 2 h post-prandial	<6.0 <7.8
Diabetes	Fasting or 2 h post-prandial	≥7.0 ≥11.1
Impaired Glucose Tolerance	Fasting and 2 h post-prandial	<7.0
		7.8-11.0
Impaired Fasting Glycemia	Fasting	6.0-6.9

(2) **Blood HbA_1c:** In 2010, the American Diabetes Association (ADA) described Glycated haemoglobin (HbA_1) as a diagnostic criterion for diabetes. The ADA selected a result of 6.5% as the cutoff value for T2DM diagnosis, assessed by the development of diabetic retinopathy, which increases steeply at ≥ 6.5%.[15]

Causes of Type 2 Diabetes mellitus

The reasons behind T2DM may be genetic or acquired. Although mutation in insulin receptors, glucose transport and signaling proteins have been identified, these are relatively rare. The acquired causes of insulin resistance include inactivity, overeating, aging, hyperglycemia and increased levels of free fatty acids (FFAs) etc. Insulin resistance is a characteristic of most T2DM and is universally true for overweight type 2 diabetic patients. Body tries to compensate this with an increased insulin secretion from pancreatic β-cells,

which leads to hyperinsulinemia.[16,17] At this stage, impaired glucose tolerance (IGT) isdetected. Eventually the β-cell compensatory response declines and relative or absolute insulin insufficiency develops in type 2 diabetes prone patients.

At this juncture, insulin secretion cannot keep pace with the underlying insulin resistance and hyperglycemia develops eventually leading to Frank T2DM. If untreated, DM carries an increased risk of macrovascular diseases such as hypertension, cardiomyopathy, myocardial infarction, strokes and microvascular diseases such as retinopathy, nephropathy and neuropathy[18,19] and these are considered to be the major causes for the mortality and morbidity among patients with T2DM.[20,21,22,23] Another cluster of problems associated with majority of T2DM patients is the visceral obesity, increased plasma lipids mainly triglycerides, small dense low-density lipoproteins(LDLs) and low levels of high density lipoproteins(HDLs), which collectively contribute to vascular complications such as hyperlipidemia, hypertension and atherosclerosis.[24]

A number of candidate genes have been identified for having roles in type 2 diabetes progression. Although several monogenic loci are associated with type 2 diabetes none has been shown to be a significant cause of the disease (i.e. >50% in all cases). Several of the genes having roles in type 2diabetes mellitus include pancreatic glucokinase (MODY 2), GLUT-2 (glucosetransporter), glucagon receptor, glucagon-like peptide-1 (GLP-1), glucokinase regulatory protein and hexokinase-1.

Recent evidence has demonstrated a role for a member of the nuclear hormone receptor superfamily of proteins in the etiology of type 2 diabetes. A relatively new classof drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferator activated receptor; PPARγ is a transcription factor and, when activated, binds to another transcription factor known as theretinoid X receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPARγ is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells (adipocytes). PPARγ is also involved in thesynthesis of biologically active compounds from vascular endothelial cells and immunecells.

Mutations in the gene for PPARγ have been correlated with insulin resistance. Itis still not completely clear how impaired PPARγ signaling can affect the sensitivity ofthe body to

insulin or indeed if the observed mutations are a direct or indirect cause ofthe symptoms of insulin resistance.

Classification of existing antidiabetic drugs and their targets

The major pathophysiological conditions of Type 2 Diabetes mellitus include (i) Decreased insulin release from β-cells, (ii) Increased secretion of glucagon from pancreatic α cells, (iii) Rise in production of glucose from liver, (iv) Dysfunction of neurotransmitters and insulin resistance in the brain cells (v) Increase in lipolysis, (vi) Rise in renal glucose reabsorption, (vii) Less effect of in the small intestine and (viii) Diminished uptake of in peripheral tissues such as skeletal muscle, liver and adipose tissue.[25] There have been tremendous advances in our understanding of the pathophysiology recognized by De-Fronzo in his Banting lecture of 2009,5 at which time he described at least eight defects in the pathophysiology of diabetes, all of which are now well-recognized but also provide appropriate treatment targets. De-Fronzo's "Ominous Octet".[26] Currently available glucose-lowering therapies target one or more of these key pathways.[27] The major classes of oral antidiabetic medications are described below (Table 2).

Table 2: Different classes of antidiabetic drugs and their molecular targets.

S.No.	Drug Class	Molecular Target	Mechanism
1	Insulin (PTP-1B)	Insulin receptor and dow-nstream regulatory proteins	Promote opening of glucose transporters through binding to Insulin receptor.
2	GSK3 Inhibitors	GSK β subunit	
3	Sulphonylureas (Glybenclamide, Netaglimide, Glyclazide, Repaglimide)	SU receptor/ K+ ATP Channel	Stimulates beta-cells to secret more insulin
4	Biguanides (Metformin)	Insulin sensitizer Unknown target	Inhibits hepatic glucose production
5	Acarbose (Inhibitor)	Alpha-glucosidase.	Delays absorption of carbohydrates by intestine
6	Thiazolidinediones[TZDs](Pioglitazone, Rosiglitazone)	PPAR-gamma transcr -iption factor	Enhances the activity of GLUT4
7	Glucagon-like peptide-1 (GLP-1) agonists	GLP-1	Promote breakdown of Glucagon
8	Dipeptidyl Peptidase-IV (DPP-IV) inhibitors	DPP-IV enzyme	Increases t1/2 of GLP-1
9	SGL2 Inhibitors	Sodium glucose cotransp-orter 2 of proximal renal tubule	Increases renal glucose elimination

(a)The α-Glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose (Precose), Voglibiose and miglitol (Glyset) function by interfering with the action of α -glucosidases present in the small intestinal brush border epithelium. The consequence of this inhibition is a reduction in digestionand the consequent absorption of glucose into the systemic circulation. The reduction inglucose uptake allows the pancreatic β-cells to more effectively regulate insulin secretion. The advantage to the use of the α -glucosidase inhibitors is that they function locally in the intestine and have no major systemic action. Hypoglycemia does not usually occur with the use of α -glucosidase inhibitors but they are effective at reducing fasting plasma glucose levels and levels of glycosylated hemoglobin (HbA1c). The common adverse side effects of these inhibitors are abdominal bloating, discomfort and diarrhea.

(b)The Sulfonylureas

The sulfonylurea and meglitinide classes of oral hypoglycemic drugs are referred to as endogenous insulin secretagogues because they induce the pancreatic release of endogenous insulin. The sulfonylureas have been used in the US for nearly 50 years. These include:

First generation Sulfonylureas: Tolbutamide, Chlorpropamide, Tolazamide.
Second generation Sulfonylureas: Glibenclamide, Gliclazide, Gliquidone.
Third generation sulfonylureas: Glimepiride.

Because all of these drugs can induce pronounced hypoglycemia, treatment is initiated with the lowest possible dose and carefully monitored until the dose is found that results in a FPGof (110-140) mg/dl. Sulfonylureas function by binding to and inhibiting the pancreatic ATP-dependent potassium channel that is normally involved in glucose-mediated insulin secretion. The main side effects of sulfonylureas are weight gain and hypoglycaemia[28], and risk is increased in people with mild to moderate renal impairment and severe hepatic impairment.

(c)The Meglitinides: The Meglitinides, repaglinide (Prandin) and nateglinide (Starlix) are non-sulfonylurea insulin secretagogues that are both fast acting and of short duration. Like the sulfonylureas, meglitinides therapy results in significant reduction in FPG aswell as HbA1c. The mechanism of action of the meglitinides is initiated by binding to areceptor on the pancreatic β-cell that is distinct from the receptors for the sulfonylureas. Like the

sulfonylureas, the meglitinides have no direct effects on the circulating levels of plasma lipids.

(d)The Biguanides: Biguanide and its derivatives for the management of diabetes have been started since middle ages. *Galegaofficinalis*, aherbaceous plant, was found to contain guanidine, galegine, and biguanide, which decreased blood glucose levels.[29] Metformin is a biguanide that is the drug of choice for the management of T2DM across all age groups. The biguanides are a class of drugs that function to lower serum glucose levels by enhancing insulin-mediated suppression of hepatic glucose production and enhancing insulin-stimulated glucose uptake by skeletal muscle. Metformin (Glucophage) is a member of this class and is currently the most widely prescribed insulin-sensitizing drug in current clinical use. Metformin administration does not lead to increased insulin release from the pancreas and as such the risk of hypoglycemia is minimal. Because the major site of action for metformin is the liver, its use can be contradicted in patients withliver dysfunction. The drug is ideal for obese patients and for younger type 2 diabetic patients.

Evidence shows that metformin improves insulin sensitivity by increasing insulinreceptor tyrosine kinase activity, enhancing glycogen synthesis and increasing recruitment and transport of GLUT4 transporters to the plasma membrane. Additionally, it has been shown that metformin affects mitochondrial activities dependent upon themodel system studied. Metformin has a mild inhibitory effect on complex I of oxidative phosphorylation, has antioxidant properties, and activates glucose 6-phosphate dehydrogenase, G-6-PDH and AMP-activated protein kinase (AMPK). The importance of AMPK in the actions of metformin stems from the role of AMPK in the regulation of both lipid and carbohydrate metabolism. In adipose tissue, metformin inhibits lipolysis while enhancing re-esterification of fatty acids**.** These include Metformin and Buformin.

(e)Thiazolidinediones: These have been proven useful in treating the hyperglycemia associated with insulin-resistance in both type 2 diabetes andnon-diabetic conditions. The Thiazolidinediones (TZDs) function as agonists for PPARγ. PPARγ is a member of a superfamily of transcription factors that also include the closely related members, PPARα and PPAR β. PPARγ exists as a heterodimer with the nuclear retinoid X receptors (RXRs).[30] The heterodimer binds to PPAR response elements in a number of target genes. Without ligand binding, the heterodimer is associated with a co-repressor complex that includes a histone deacetylase. Deacetylated histone keeps DNA in a transcriptionally repressed state.[31] When

ligand binds to PPARγ, the co-repressor complex dissociates and a co-activator complex containing histone acetylase associates resultingin chromatin structural changes and transcriptional activation. The net effect of the TZDsis a potentiation of the actions of insulin in liver, adipose tissue, skeletal muscle, increased peripheral glucose disposal and a decrease in glucose output by the liver [32]. Thiazolidinediones are associated with an increased fracture risk [33] and in some patients may have led to heart failure.[34]

Genes shown to be affected by PPARγ action include those encoding glucokinase, GLUT4, malic enzyme, lipoprotein lipase, fatty acyl-CoA synthase and adipocyte fattyacid binding protein.[35] PPARγ is predominantly expressed in adipose tissue, the effects ofPPARγ agonists seen in the liver and skeletal muscle may be exerted via endocrine signaling from adipocytes. Recently it was shown that mutations in the PPARγ genewere correlated to familial insulin résistance.[32] These include Rosiglitazone and Pioglitazone.

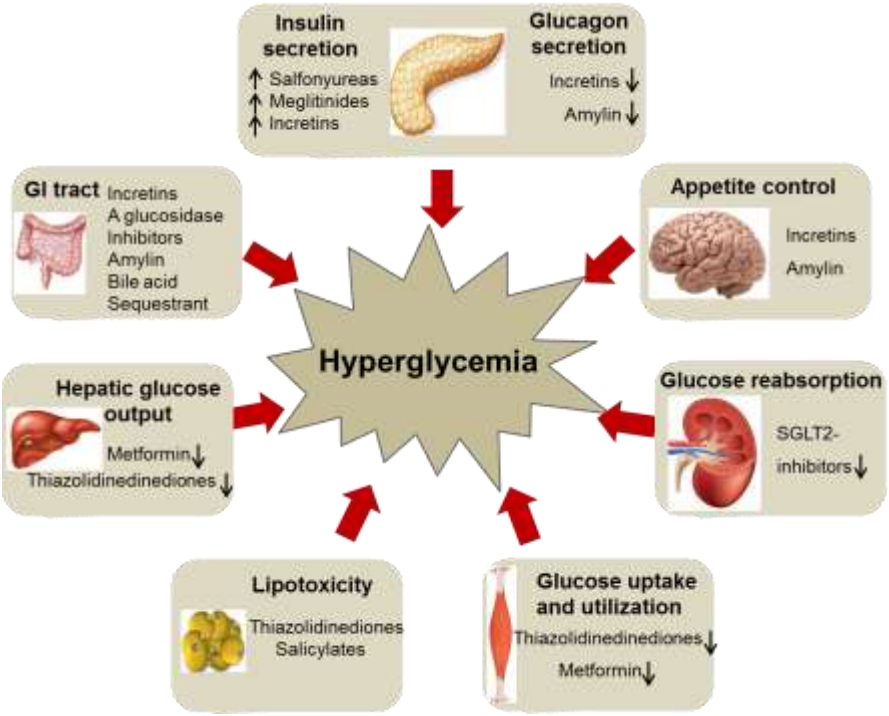

Figure 2: Sites of action of the current therapies for the treatment of type 2 diabetes mellitus.

Novel antidiabetic drugs targeting the incretin axis

(a) Glucagon-like peptide-1 (GLP-1) agonists: The primary metabolic responses to GLP-1 release are inhibition of glucagon secretion and rise of glucose-dependent insulin release from the pancreas, both effects leading to reduced glucose release. The GLP-1 secretion is

controlled by L-cells of gut. The hormonal action of GLP-1 is rapidly terminated as a result of enzymatic cleavage by DPP IV. Recent clinical evidence has indicated that either infusion of GLP-1 or inhibition of DPP IV can result in profound reductions in plasma glucose concentrations, decrease in HbA1c and improvement in function of pancreatic β-cells.GLP-1 is metabolized extremely rapidly in the circulation, with a in *vivo* half-life of less than 2 min. and is the probable explanation for the short-lived effect of single doses of native GLP-1. GLP-1 is rapidly inactivated by amino terminal cleavage at penultimate alanine residue to generate inactive GLP-1 amide (9-36). This residue is important for receptor activation and pharmacological studies with this metabolite suggest that it behaves as a functional antagonist at the pancreatic receptor.[36,37,38,39,40,41,42] Thus, both represent important targets for the treatment of the hyperglycemia associated with diabetes and insulin resistance.[43]

Current use of GLP-1 mimetic or GLP-1 receptor (GLP-1R) agonists emphasizes on peptides that must be injected. *Byetta* (developed by Amylin Pharmaceuticals and Eli Lilly and Co.) is the most promising GLP-1R agonists is a derivative of exendin-4, a peptide from salivary gland. Another promising GLP-1R agonist is liraglutide that is a fatty acid-linked derivative of GLP-1. Liraglutide is found to be resistant to DPP IV cleavage.

(b) Dipeptidyl Peptidase-IV (DPP-IV) inhibitors

Inhibition of DPP-IV through targeted compounds would seem like ideal strategy for treatment of the hyperglycemia during diabetes mellitus, but there are several side effects associated with DPP IV inhibition.[44] Prolonged inhibition of DPP IV enzymatic activity may have unexpected consequences unrelated to control of hyperglycemia[45] due to the fact that GLP-1 and GIP are the only known substrates of DPP-IV. DDP IV inhibitor developed by Merck, *Januvia* (sitagliptin) has recently been approved for use alone or in combination with either metformin or thethiazolidinediones (TZDs). Treatment of patients with Sitagliptin as the only therapeutic agent for 4.5 months produced significant decrease in HbA1c along with significant improvement of β-cell function. There is no change in body weight with the administration of Sitagliptin.

DPP IV was first recognized as cell surface antigen in lymphocyte as CD26. The functions of CD 26 are mediated through many pathways that are not directly related to its cleavage activity. It harbors properties of adenosine deaminase-binding (ADA) and have role binding to extracellular matrix. However, the knockout mice lacking CD26 have shown increased insulin secretion and improved glucose tolerance.[46]

The major clinical advantage for using DPP IV inhibitors is that these can be orally delivered during clinical trials. The drug NVP DPP728 was shown to be potent DPP IV inhibitor that led to significant lowering in blood glucose and HbA1c levels. LAF 237 is a second generation DPP IV inhibitor that is currently in clinical trials. Sitagliptin, linagliptin, saxagliptin, vildagliptin are other potent DPP IV inhibitors that are currently administered in Type 2 diabetes mellitus.

DDP IV inhibitors have a low risk of hypoglycaemia and do not lead to weight gain due to their mechanism of action.[47]

(c) Inhibitors of enzymes involved in insulin signaling (PTP1B, GSK3, etc)

Insulin induces an array of biological responses through binding to its insulin receptor.[48] The insulin receptor (IR) is a heterotetrameric protein consisting of two extracellular α-subunits and two transmembrane β-subunits. The binding of the ligand to the α subunit of IR induces conformational changes in the receptor, which in turn stimulates the tyrosine kinase activity intrinsic to the β-subunit of the IR.[49] Extensive research have shown that receptor auto phosphorylation and phosphorylation of plays significant role for the proper and complex functions of insulin leading to several cellular responses.[50,51,52,53] Several immediate substrates (on Tyr residues) including insulin receptor substrates IRS proteins 1 – 4, Shc, and Gab 1, each of which have specific docking sites for other signaling proteins containing SH2 domains are trans phosphorylated by Insulin receptors.

These events lead to the activation of downstream signaling molecules including phosphatidylinositol-3-kinase (PI-3-kinase). Research have suggested that PI-3-kinase plays significant role in the metabolic action of insulin. However, the discrete pathways which couple PI-3-kinase to glucose regulation remain poorly defined. Protein kinase B(PKB or AKT) is a Ser/Thrkinase that is dependent on PI-3-kinase for insulin-mediated activation of glucose transport and glycogen synthesis.

Insulin is essential for maintaining glucose homeostasis and regulating carbohydrate, lipid, and protein metabolism. The central role of the insulin receptor in the control of metabolism and growth has been confirmed in insulin receptor null mouse models.[54,55] Decreased cellular responses to insulin or perturbation of the insulin signaling pathways are associated with several pathological conditions.

Mutations in insulin receptor gene which lead to alterations of receptor synthesis, degradation, and function have been described in patients with several uncommon syndromes associated with severe insulin resistance. The molecular basis for insulin resistance associated with type 2 diabetes remains poorly understood. However, several studies have shown modest decrease in number of insulin receptor that is attributed to downregulation in the response to hyperinsulinemia in tissues or cells from type 2 diabetic patients.[56,57] Substantial decreases in receptor tyrosine kinase activity and an even more profound defect in receptor-mediated IRS phosphorylation or PI-3-kinase activation have been described through tissue samples (e.g. muscle or fat) from rodents or human subjects with type 2 diabetes mellitus.[58,59] Although controversial, diminished activation of Akt was reported in skeletal muscle from type 2 diabetic patients.[60] Thus, pharmaceutical intervention through augmentation of insulin receptor function may ultimately benefit patients with diabetes.[61]

Glycogen synthase kinase 3 (GSK-3) is a cytoplasmic serine/theronine kinase that plays key roles in insulin signaling and metabolic pathways. This enzyme also has a key role in Wnt-β catenin signaling that is critical during embryonic development to know about the cell fate [62]. GSK-3 is active in the absence of insulin and it phosphorylates (and thereby inhibits) glycogen synthase and several other substrates are phosphorylated through GSK3. Insulin binding to the receptor activates a phosphorylation cascade, leading to inhibitory phosphorylation of GSK-3 by Akt. Thus, glycogen synthase is activated through insulin by promoting its dephosphorylation through the inhibition of GSK-3.[63]

Lithium have antidiabetic affect through inhibiting GSK-3 and have been shown to activate glycogen synthase in cells. This antidiabetic effect of Lithium have been tested in animal models of diabetes, suggesting that specific inhibitors of GSK-3 hold the potential as novel therapeutics for diabetes.[64]

Novel antidiabetic drugs targeting renal glucose

(a) Sodium Glucose Cotransporter-2 Inhibitors (SGLT-2): Sodium glucose cotransporter inhibitors include canagliflozin, dapagliflozin. These provide insulin independent glucose lowering by blocking glucose reabsorption proximal renal tubule by inhibiting SGLT2. More glucose is excreted in the urine through blocking these transporters. SGLT2 inhibitors decrease the blood glucose, but these have the risk of causing hypoglycaemia. These SGLT2 inhibitors may lead to decreased blood pressure and dehydration, mainly in the patients administered on diuretics.[65]

CONCLUSION

Type 2 DM is a metabolic disease that can be prevented through lifestyle modifications, diet restrictions and regulation of body metabolism. Education of the populace and dissemination of information regarding the long term harmful effects related to diabetes mellitus will play significant role in the control of this emerging epidemic. Several antidiabetic drugs are available in the market and new ones is still in clinical trials, yet no cure is available for the disease, despite new insight into the pathophysiology of the disease. Disease management should be tailored to improve the quality of life of individuals with type 2 diabetes mellitus. The present available antidiabetic drugs available in market are targeted against one or other enzymes involved in glucose metabolism. New drugs are being developed that targets the insulin receptors and downstream protein associated with insulin signal transduction pathway. The prevalence of diabetes is increasing tremendously in the present time, so there is an urgent need to find novel target based drug molecules in order to inhibit the progression of the disease. Research in this area is going on to find some potent antidiabetic molecules that can treat the symptoms and serious abnormalities associated with the disease including cardiovascular problems like high blood pressure, atherosclerosis, etc. Combination therapy is also coming out to be a future strategy in which two or more antidiabetic drugs are mixed in a specific ratio in order to obtain an optimum effect.

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