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CURRENT STATUS ON ORAL ANTIDIABETIC AGENTS: A REVIEW

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ABSTRACT
Diabetes is a chronic disease marked by high levels of sugar in the blood. Proper control of blood sugar in type 2 diabetes mellitus (T2DM) is not adequate till now in spite of use of well planned dosage regimens containing oral hypoglycemic agents. Despite evidence that glycemic control as well as control of other cardiovascular disease (CVD) risk factors such as hypertension and dyslipidemia decreases morbidity and mortality in the diabetic population, control of glycemia and other CVD risk factors remains largely suboptimal making the concept of prevention of diabetes very appealing to control CVD risk, especially that such a risk is already increased in people in the prediabetic stage. Several large controlled trials have been completed testing various options for diabetes prevention. In this paper we a tired to present an update on preventive measures of type 2 diabetes and highlighting the major recent trials completed to date in this very important area of investigation.

KEYWORDS : *Diabetes, Obesity, Sulfonylureas, Biguanides, Alpha-Glucosidase inhibitors, Thiazolidinediones, Meglitinides, Glucagon like peptide, DPP-4 inhibitors, PPAR-γ phosphorylation inhibitors, Sodium–glucose co-transporter-2 inhibitors.*

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INTRODUCTION

Noninsulin dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by an elevated blood glucose level that results from inadequate insulin action in insulin sensitive tissues and from abnormal insulin secretion. T2DM affects 6% of the population. Approximately 197 million people worldwide have impaired glucose tolerance. [1] Most common cause for this abnormality is because of obesity and the associated metabolic syndrome. This number is expected to increase to 420 million by 2025. Insulin is an anabolic hormone that exerts its action on glucose and lipid metabolism at multiple points. Its metabolic effects include: (a) attenuation of gluconeogenesis and promotion of glycogen synthesis in the liver, (b) facilitation of glucose uptake by peripheral tissues,

(c) inhibition of lipolysis in adipose tissue. Insulin inhibits hepatic glucose production by regulating genes of the gluconeogenic and glycogen synthesis pathways at the transcriptional and post transcriptional levels. In muscle and adipose tissue, insulin accelerates the uptake of glucose by facilitating the translocation of the glucose transporter GLUT-4 to the cell membrane. In adipose tissue, insulin blocks triglyceride breakdown by inhibiting hormone sensitive lipase such that, in a fed state, high levels of insulin promote triglyceride accumulation whereas, in fasting or 'fight or flight' situations, triglycerides are broken down to yield fatty acids, which are then used by other tissues[1].

Obesity is the result of imbalance between energy intake and energy expenditure. Environmental factors, such as the general availability of high calorie food or the limited need for physical exercise and genetic factors that predispose to weight gain contribute to the development of obesity. Obesity is a rapidly growing nutritional disorder characterized by excessive accumulation of adipose tissue. Both hyperplasia and hypertrophy of fat cells are found when weight gain takes place. In diabetes mellitus, on the other hand, two main defects are found; insulin resistance of peripheral tissues such as liver, muscle and fat as well as secretory failure of pancreatic cells. Increased body weight is tightly associated with insulin resistance and T2DM. Regulation of adiponectin in obesity, insulin resistance and by insulin modulating hormones and drugs is well established. (Shown in fig.1) Thus, adiponectin levels are significantly decreased in insulin resistance and obesity. Furthermore, adiponectin expression and secretion increase when insulin sensitivity and obesity improve. Insulin sensitizing thiazolidinediones (TZDs) probably mediate part of their effect *via* adiponectin since they increase plasma concentrations of this adipokine in both, subjects with normal insulin sensitivity and T2DM. In contrast, various hormones associated with insulin resistance and obesity including catecholamines, insulin, glucocorticoids, tumor necrosis factor alpha (TNF-alpha and interleukin-6 (IL-6) down regulate adiponectin expression and secretion.

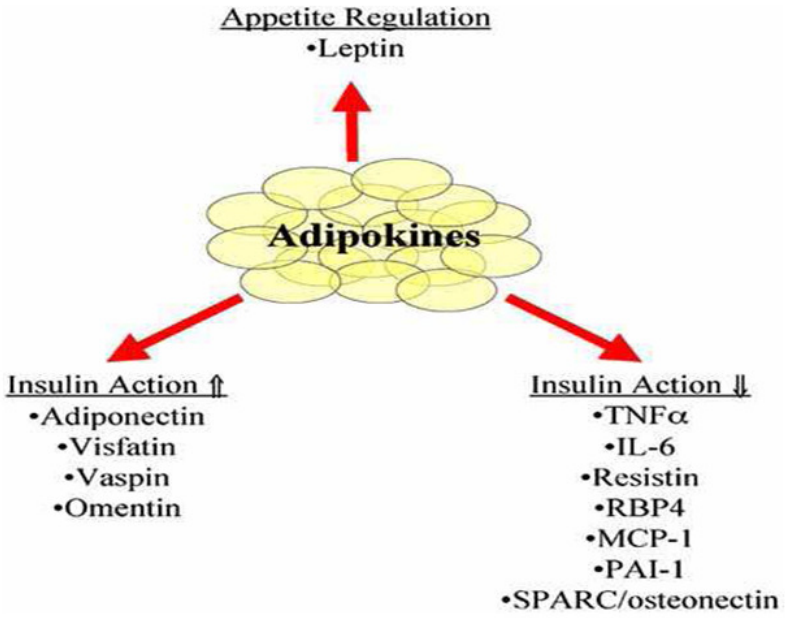

Fig.1 Adipokines implicated in insulin sensitivity and appetite control [2]

Various molecular targets available for antidiabetic drugs and their different functions are listed below

Table 1 Molecular targets and their main function in T2DM [3]

Target	Function
Insulin secretagogue	Enhance insulin secretion from pancreatic β cells, promote islet proliferation and suppress glucagon release.
GLP-1, GLP-1 receptor agonists	
Improving insulin action Resistin	Potential inhibitor of insulin sensitivity. Negative regulator of insulin signaling through dephosphorylation of insulin. Negative regulator of insulin signaling.
Protein-tyrosine phosphatase-1B Type II SH2- domain-containing inositol 5-phosphatase.	
Inhibition of hepatic glucose production	Enhances hepatic glucose output. Catalyzes the first step of glycolysis. Regulator of glycolytic and gluconeogenic rates through production of fructose-2,6-bisphosphate. Catalyzes the last step of gluconeogenesis Regulates gluconeogenic rates. Catalyses the conversion of glycogen to glucose-1-phosphate monomers. Inhibits glycogen synthase.
Glucagon Glucokinase 6-phosphofructo-2-kinase/fructose-2,6 bisphosphatase Glucose-6-phosphatase Fructose-1,6-bisphosphatase Glycogen phosphorylase Glycogen synthase kinase	
Strategies altering lipid metabolism	Enhances fatty acid oxidation and inhibits hepatic glucose output. Enhances fatty acid oxidation in liver and skeletal muscle, enhances translocation of GLUT4 in muscle and inhibits lipolysis in adipose tissue. Enhances insulin action in adipose tissue Regenerates active glucocorticoids.
Adiponectin AMP-activated protein kinase Insulin expression in adipose tissue 11-hydroxysteroid dehydrogenase type 1	

TABLE 2 Principal limiting factors in the use of currently available anti diabetics[4]

AGENT	HYPOGLYCEMIA	WEIGHT GAIN	OTHERS
Insulin or insulin Analogues	_	_	Injection
Sulfonylureas	_	_	_
Glinides	_	_	_
Biguanides	No	No	Lactate Production
Glitazones	No	_	Fluid Retention
R-GLUCOSIDASE Inhibitors	No	No	GI side effect

Classifications of Antidiabetic Drugs.

Sulfonylurea's [5,6]

Sulfonylureas have remained the main stay of antidiabetic therapy since the early 1950s.The use of the first generation sulfonylureas

(Acetohexamide, Chlorpropamide, Tolbutamide and Tolazamide) quickly fell out of favor.

Supporting the benefits of the sulfonylureas as well as the availability of newer generation. sulfonylurea with more favorable side effect profiles have contributed to their renewed popularity.Sulfonylureas work by stimulating insulin release from the beta cells of the pancreas and may slightly improve insulin resistance in peripheral target tissues such as muscle and fat. On average, this class reduces glycosylated hemoglobin A1c (HbA1c) levels by 0.8 to 2.0 percent and fasting plasma glucose (FPG) concentrationsby 60 to 70 mg per dL with the greatest reductions observedin patients with the highest FPG concentrations at the initiation of therapy. Hypoglycemia is the most worried side effect of the sulfonylureas. It is of particular concern with agents that are metabolized to an active metabolite with significant renal excretion. These agents include Chlorpropamide and Glyburide, both of which should be avoided in the setting of impaired renal function and used with caution in elderly patients. Glipizide and Glimepiride are associated with a lower incidence of hypoglycemia. All sulfonylureas have been associated with weight gain and thus, may not be the optimal first choice for obese patients.

Treatment failure with sulfonylurea therapy can be divided into two categories: primary and secondary. Primary failure results when a patient exhibits an initial poor response to sulfonylurea therapy. Approximately 20 to 25 percent of patients with type 2 diabetes will demonstrate primary failure to sulfonylurea therapy. Secondary failure results when the patient responds well to treatment initially (a decrease in FPG of greater than 30 mg per dL but eventually the treatment fails to maintain adequate control. This phenomenon is reported to occur in approximately 5 to 10 percent of patients per year.

Biguanides[5,6]

These lower the production of glucose that is made in the liver. It also makes the body more sensitive to insulin. Cholesterol levels may be lowered as well. Metformin is currently the only agent in this class available for the treatment. Metformin works by reducing hepatic glucose output and to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues. Metformin has been shown to reduce HbA1c levels by approximately 1.5 to 2.0 percent and FPG levels by 50 to 70 mg per dL. Other effects include a reduction in plasma triglyceride levels and low density lipoprotein (LDL) cholesterol levels. On the whole, Metformin has a favorable side effect profile. Most of the related side effects (such metallic taste, gastrointestinal discomfort and nausea) are transient and commonly reported only during initiation of therapy. Slow dosage titration is recommended to lesser these effects. Taking the drug with meals may also lesser the severity of the gastrointestinal side effects.

Alpha Glucosidase Inhibitors[5, 6]

These delay the conversion of carbohydrates into glucose during digestion. This prevents blood glucose levels from reaching too high. Acarbose and Miglitol are the two agents available in this class. Alpha glucosidase inhibitors act by inhibiting the enzyme alpha glycosidase found in the brush border cells that line the small intestine, which cleaves more complex carbohydrates into sugars. Because they inhibit the breakdown and subsequent absorption of carbohydrates from the gut following meals, the largest impact of these drugs is on postprandial hyperglycemia. Their effect on FPG levels are modest. They have been associated with a reduction in HbA1c by 0.7 to 1.0 percent and FPG levels by 35 to 40 mg per dL. Thus, these agents are most useful in patients who have mild FPG elevations or in patients with predominant postprandial hyperglycemia. The most side effects observed with these agents are gastrointestinal, including abdominal discomfort, bloating, flatulence and diarrhea but are reversible with discontinuation.

Thiazolidinediones[7]

Sensitizes muscle and fat cells to accept insulin more easily.The discovery of perioxisome proliferator activated receptor (PPAR) and their subtypes have led to the discovery of a new generation of drugs. The two major PPAR receptors

are α& γ and both are expressed by obligate hetero dimerisation with retinoic acid x receptor (Rx Rα and Rx Rγ). The PPAR (α) is primarily responsible for lipolysis by activation of enzymes such as acylCOA oxidase, lipoprotein lipase, malic enzyme, bifunctional enzyme and medium chain acylCOA dehydrogenase. On the other hand, PPAR(γ) is primarily responsible for the adipocyte differentiation and at the metabolic level, in FFAand lipid anabolism and storage. The pronounced hypoglycemic effect seen by PPAR(γ) agonists is attributed primarily to adiposite differentiation and activation. The PPAR(γ) agonists Ciglitazone, Pioglitazone,Englitazone, Troglitazone and Rosiglitazone are of the members of this class. They decrease hepatic glucose output and increase peripheral glucose utilization by improving insulin sensitivity at hepatic and muscle sites.They restore the sensitivity of phosphophenol pyruvate carboxy kinase (PEPCK) to insulin thereby decreasingglycogenolysis. They also increase peripheral triglyceride clearance and decrease hepatic triglyceride synthesis, independent of insulin. At the cellular level, they increase the binding and tyrosine kinase activity of insulin receptors, activate post receptor signaling proteins and enhance insulin induced translocation of GLUT-4 on to the plasma membranes. All these effects are dependent on insulin. These agents do not stimulate insulin secretion from β cells and are therefore not effective in insulinopenic subjects.

Meglitinides[8]

These stimulate insulin production when there is glucose present in the blood. If blood sugar is low, the drug does not work as well. Repaglinide is a new non sulfonylurea insulin secretagogue agent, the first available from the meglitinides class. Nateglinide the newest member of the class, has recently become available. The mechanism of action of the meglitinides closely resembles that of the sulfonylureas. The meglitinides stimulate the release of insulin from the pancreatic beta cells. However, this action is mediated through a different binding site on the "sulfonylurea receptor" of the beta cell and the drug has somewhat different characteristics when compared with the sulfonylureas. Unlike the commonly used sulfonylureas, the meglitinides have a very short onset of action and a short half life. Repaglinide has shown similar effects on HbA1c and FPG levels when compared with Glyburide,0.5 to 2 percent and 65 to 75 mg per dL respectively.

Some potential advantages of this class of agents include a greater decrease in postprandial glucose and a decreased risk of hypoglycemia.

Glucagon like peptide 1 (GLP1)[9]

Ingestion of a meal stimulate secretion of incretin hormones, such as glucose-dependent insulin tropic polypeptide (GIP) and glucagon like peptide 1 (GLP1) are released by duodenal K cells and L cells. Incretins stimulate pancreatic insulin secretion and concomitantly inhibit glucagon release from pancreatic islets. Besides its peripheral action, GLP1 signals to the brain and reduces food intake. Owing to its post prandial glucose lowering effect and its potent insulin secretory effect, GLP1 has been a well developed drug target for the treatment of T2DM.

Exenatide and AVE0010 are GLP-1 mimetics or analogues with longer half life proved to be beneficial. Besides the important effect of incretins in regulating insulin secretion from β-cells, expression of GLP1 and GIP has recently been demonstrated in the CNS, where their receptors are located in the hypothalamic arcuate, paraventricular and supraoptic nucleus as well as the brainstem and involve in the regulation of food intake. Furthermore, by binding to their central receptors, GLP1 and GIP improve glucose homeostasis in peripheral tissues such as liver, skeletal muscle and pancreas. Overall combined peripheral and central GLP1 action provides an important approach to improve glucose homeostasis. Liraglutide & Lixisenatide, a once-daily human GLP-1analogue, improves pancreatic β-cell function and arginine stimulated insulin secretion during hyperglycaemia in patients with T2DM. An important regulator of the biological activity of GLP-1 is N-terminal degradation by the common endogenous amino peptidase enzyme; dipeptidyl peptidase-4(DPP-4). This enzyme removes the two N terminal amino acids histidine

and alanine from GLP-1,yielding the N-terminally truncated form, GLP-1 amide. This metabolite of GLP-1 is inactive in stimulating insulin secretion or reducing glucose levels and may even be an antagonist or partial agonist for theGLP-1 receptor.

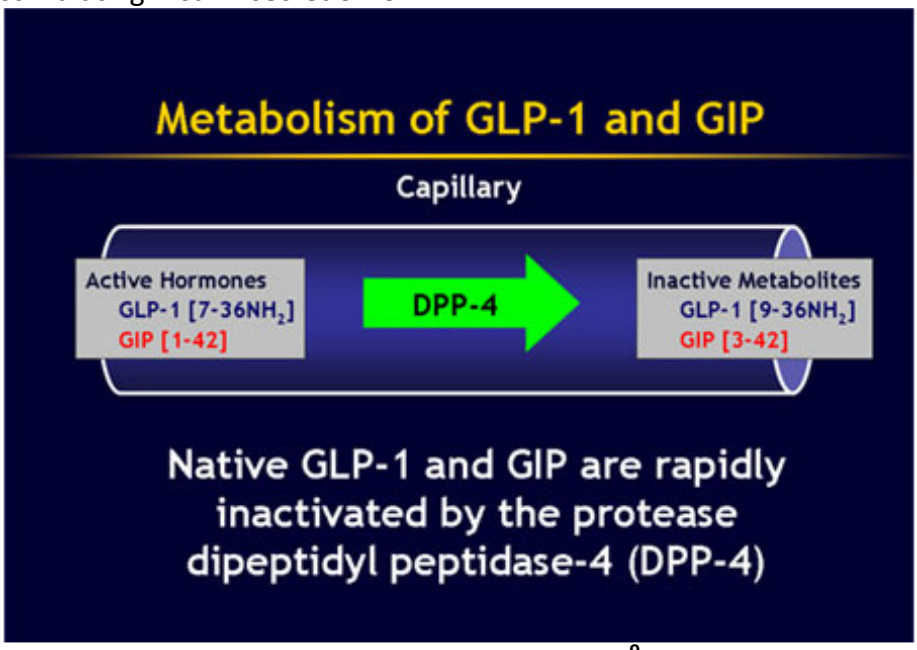

Fig. 2 Metabolism of GLP-1[9]

Hence, the metabolism of GLP-1 by DPP-4 is largely considered to be an inactivation processes (shown in Fig. 2) The efficiency of DPP-4 is high, resulting in such a rapid metabolism of GLP-1that the half life of circulating peptide is very low, approximately 1–2 min.

TABLE 3-GLP-1 mimetics under development[9]

Compound	Half Life	Role
Exenatide	4–5h	Inherent in exendin 4amino acid sequence
Liraglutide	11–15h	Self-association andalbumin binding
CJC-1131	10–12 days	In vivo covalentconjugation to albumin
ZP-10	-	Inherent in exendin 4sequence and addedC-terminal stability
Albugon	-	Genetic fusion proteinwith albumin
BIM-51077	-	Enzymatically stabilized GLP-1 analogue

Dipeptidyl Peptidase- 4 (DPP-4) inhibitors:[10]

DPP-4 is a glycoprotein consisting of 766 amino acids in humans. It is a protease with the catalytic site occurring in the C-terminal extracellular end of the sequence. A number of bioactivepeptides are substrates for DPP-4, most of them are neuro-peptides which include substance P, gastrin releasing peptide, neuropeptide Y and pituitary adenylate cyclase activating peptide (PACAP). GLP 1,GLP 2 and glucose dependant insulin tropic peptide are also cleaved by DPP-4. Hence, high specificity for DPP-4 would be advantage to avoid inhibition of degradation of substrate

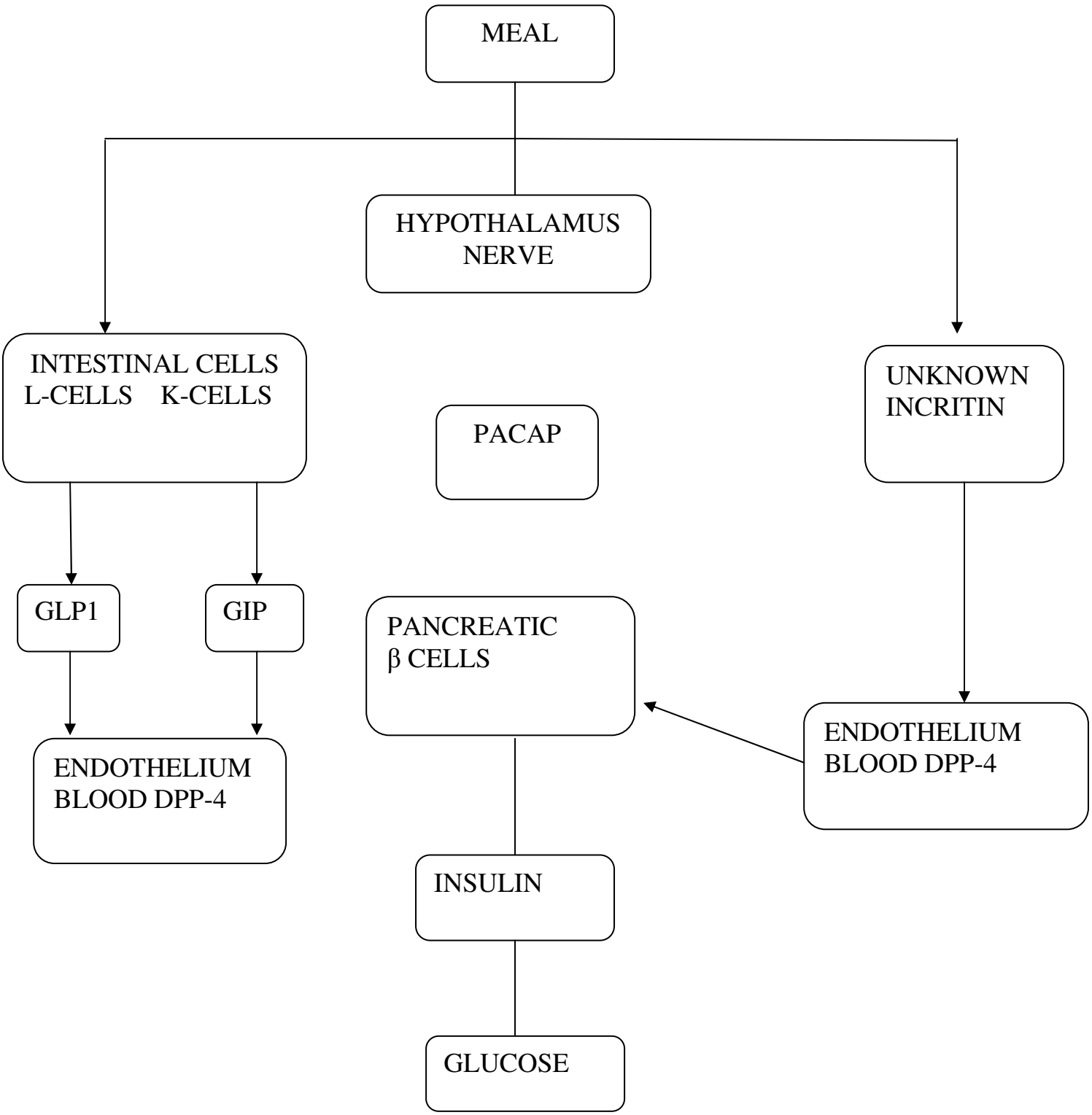

Fig.3- Schematic representation of Role of DPP-4[10]

DPP-4 inhibitors are novel class of antidiabetic drugs having potential to increase β cell function and clinical course of Type 2 diabetes mellitus. These produce no weight gain. Main advantages of drugs are they are given orally with very less gastrointestinal side effects like vomiting and nausea. To overcome the increasing problem of Type 2 diabetes mellitus, DPP-4 inhibitor is the most useful way to treat it. Mainly these drugs are given orally and most of drugs are target specific.

These agents are having some drawbacks due to its action on peptide YY, GHRH, Neuropeptide Y etc. But these effects are negligible as compared to its antidiabetic activity. This drug inhibits enzyme dipeptidyl peptidase which causes the metabolism of GLP-1 which is responsible for insulin secretion.(fig.3). DPP-4inhibitors drugs like Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin and Alogliptin are used nowadays. Sitagliptin is drug approved by US FDA in 2006. Other drugs are in late phases of clinical trials.

So there is necessary to make research on these DPP-4 inhibitors and to produce some more analogues because they have ability to restore insulin secretion with increasing β-cell mass.

1) Sitagliptin

It was approved by US FDA in Oct. 2006 used as alone or with metformin. It was introduced in US market in 2006 and in Europe in 2007.Generaly primary importance is selectivity. Sitagliptin exhibits > 2600 time's higher affinity for DPP-4 than structurally related DPP-7 and DPP-9 enzymes. In phase-I drug-drug interaction studies, Sitagliptin did not alter the pharmacokinetic of other oral hypoglycemic agents including Metformin or Sulphonylureas and these drugs did not alter the pharmacokinetic properties of Sitagliptin.

2) Vildagliptin

It is in late phase clinical development. It is used as mono therapy or in combination with Metformin, Pioglitazone. Most common adverse effects are nasopharyngitis, headache and dizziness. It is also give some episodes of hypoglycemia.

3) Saxagliptin

These drugs are used single or in combination with other hypoglycemic drugs. In combination they are used with Metformin or Tthiazolidinediones.

4) linagliptin[10,11]

Is a DPP-4 inhibitor developed by Boehringer Ingelheim for treatment of type II diabetes. Linagliptin was approved by the US FDA on 2 May 2011 for treatment of type II diabetes. It is being marketed by Boehringer Ingelheim and Lilly. Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulin tropic polypeptide (GIP). Both GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Thus, Linagliptin stimulates the release of insulin in a glucose-dependent manner and decreases the levels of glucagon in the circulation.

5)Alogliptin

A study of Alogliptin doses ranging from 25 to 800 mg in healthy male subjects showed rapid absorption and slow elimination. Approximately 60% to 70% of Alogliptin was excreted unchanged in the urine. Mean peak DPP-4 inhibition ranged from 93% to 99%, and mean inhibition at 24 hours after dosing ranged from 74% to 97%, depending on the dose like sitagliptin, alogliptin is not significantly metabolized and is primarily excreted by the kidneys.

TABLE 4-DPP-IV inhibitors in various clinical phases[12]

Company	Compound Code	Type of Inhibition	Rate of absorption	*T*1/2 (hrs)	Activity level	Enzyme Inhibition
Novartis	LAF-237 NVP-DPP728	Covalently Modifying	Slow	>4	Constantly High	Long-lasting
GlaxoSmithKline	GW-229A	Covalently Modifying	Slow	>4	Constantly High	Long-lasting
Bristol-Myers Squibb	BMS-477118	Covalently Modifying	Slow	>4	Constantly High	Long-lasting
Merck	MK-0431	Non-covalent	Rapid	2–7	Highly	Short-lived

		Reversible			Variable	
Probiodrug	P32/98 P93/01 =PSN9301	Non-covalent Reversible	Rapid	2–7	Highly Variable	Short-lived

PPARγ-phosphorylation Inhibitors[13]

Obesity induced in mice by high fat feeding activates the protein kinase Cdk5 in adipose tissues. This results in phosphorylation of the nuclear receptor PPARγ(peroxisome proliferator-activated receptor-γ), a dominant regulator of adipogenesis and fat cell gene expression, at serine 273. This modification of PPAR-γ does not alter its adipogenic capacity, but leads to dysregulation of a large number of genes whose expression is altered in obesity, including a reduction in the expression of the insulin sensitizing adipokine, adiponectin. The phosphorylation of PPAR-γ by Cdk5 is blocked by anti-diabetic PPAR-γ ligands, such as Rosiglitazone. This inhibition works both *in vivo* and *in vitro*, and is completely independent of classical receptor transcriptional agonism.

Similarly, inhibition of PPAR-γ phosphorylation in obese patients by rosiglitazone is very tightly associated with the anti-diabetic effects of this drug. All these findings strongly suggest that Cdk5-mediated phosphorylation of PPAR-γ may be involved in the pathogenesis of insulin-resistance, and present an opportunity for development of an improved generation of anti-diabetic drugs through PPAR-γ.

Sodium glucose co transporter-2 inhibitors [14]

Sodium coupled glucose co transporters (SGLTs) couple the transport of glucose against a concentration gradient with the simultaneous transport of Na+ down a concentration gradient. Two important SGLT (SGLT1 and SGLT2) have been cloned and identified, SGLT1 and SGLT2, while an additional four have been proposed as part of the SCL5gene family. SGLT1 is located primarily in small intestinal cells but is also present in the kidney and the heart where its expression regulates cardiac glucose transport. SGLT1 is a high-affinity, low-capacity transporter and therefore accounts for only a small fraction of renal glucose reabsorption; it serves predominantly as a sodium-glucose/galactose co-transporter. Genetic mutations in the SGLT1gene result in glucose and galactose malabsorption. In contrast, SGLT2 is a low-affinity, high capacity SGLT located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule (S1 segment). Ninety percent of filtered glucose is reabsorbed by SGLT2; the other 10% is reabsorbed by SGLT1 in the late proximal straight tubule.(shown in fig.4). Competitive inhibition of SGLT2 therefore represents an innovative therapeutic strategy for the treatment of hyperglycaemia and/or obesity in patients with type 1 or type 2 diabetes by enhancing glucose and energy loss through the urine. Sodium glucose co-transporter type 2 inhibition is a novel treatment option for diabetes, which has been studied in preclinical models and a few potent and selective SGLT2 inhibitors have been reported and are currently in clinical development. These agents appear to be safe and generally well tolerated, and will potentially be a beneficial to oral anti hyperglycemic agents.

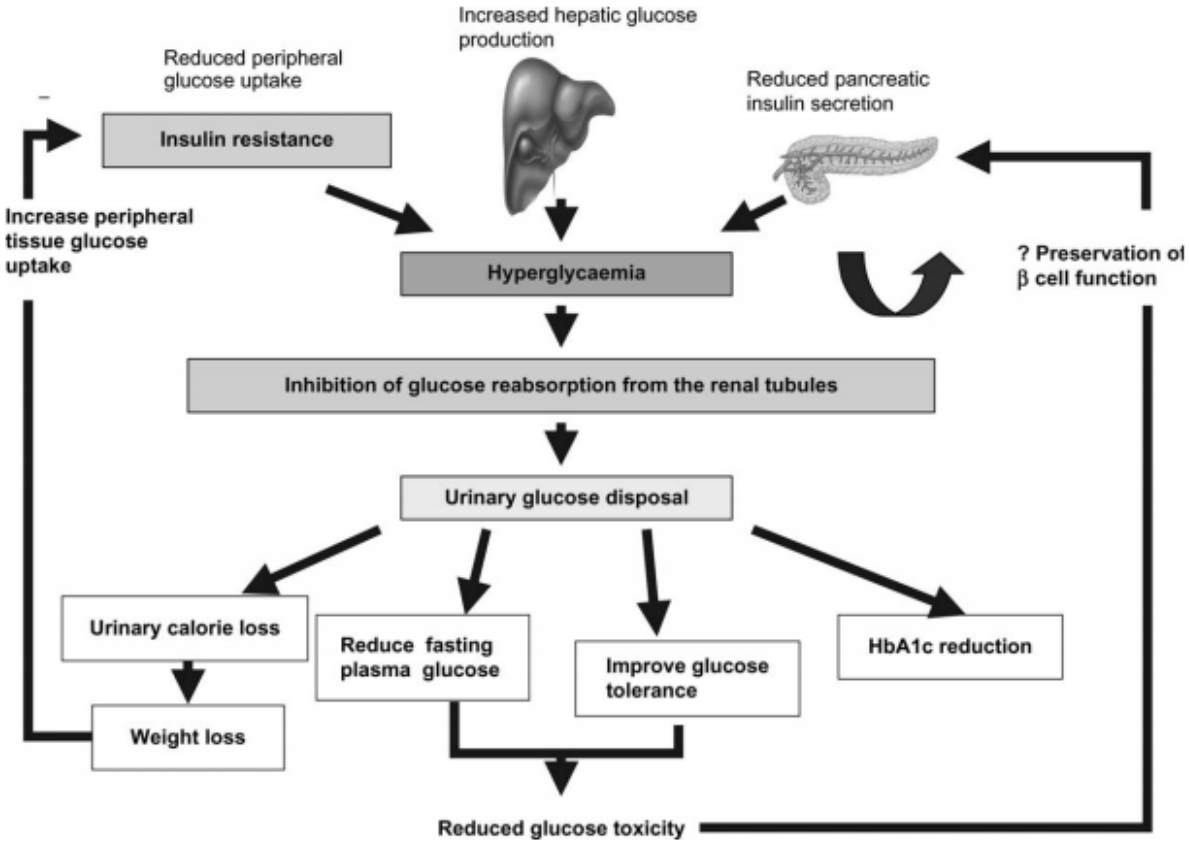

Fig. 4 Schematic representations of clinical effects of SGLT 2 inhibitor[14]

Pipeline products[15]

Drug Name	Company Name	Clinical Trial Stage
ALS 2-0426	Alantos Pharmaceuticals, Amgen, Servier	1
PSN9301	OSI	2
SYR-322	Takeda	3
R1579	Roche	1
MP-513	Mitsubishi Pharma	2
Gastrin + DPP IV Inhibitor	Transition Therapeutics	Preclinical
Saxagliptin	Otsuka Pharmaceutical Co, Bristol-Myers Squibb	3
Insulin sensitizer		
ISIS 113715	Isis	3
NCX 4016 (Nitric Oxide donating derivative of Acetyl Salicylic acid)	NicOx	2
DG070 inhibitors	Develogen AG	Preclinical
Biguanides		
Gastrin + Metformin	Transition Therapeutics	1
GLP 1 Analogue / Agonists		
Abiglutide (716155)	glaxosmithkline	2

TH0318	Theratechnolgies	1
Liraglutide (NN2211)	Novo Nordisk	3
R1583	Roche	2
Oral GLP	Emisphere Technologies	1
Exendin-4	ConjuChem	2
AVE0001A	Sanofi Aventis	2
Gastrin +GLP 1 Agonist	Transition Therapeutics	2
Peroxisome Proliferator-Activated Receptor (PPAR) agonist/analogue		
CS-011 (Rivoglitazone)	Sankyo	2
Metaglidasen(MBX 102)	Metabolex	2
MBX-2044	Metabolex	1
AVE8134	Sanofi Aventis	2
AVE0897	Sanofi Aventis	1
R1439, aleglitazar	Roche	2
AVE0847	Sanofi Aventis	2
SAR351034	Sanofi Aventis	Preclinical
376501	Glaxosmithkline	1
625019	Glaxosmithkline	1
677954	Glaxosmithkline	2
Avandia	Glaxosmithkline	2
Avandia XR	Glaxosmithkline	2
PPAR γ Agonist + simvaststin	Glaxosmithkline	3
MCC-555, Netoglitazone	Mitsubishi Pharma, Novartis	
Muraglitzar	Bristol-Myers Squibb	3
R483	Roche	2
PPM-204	Wyeth, Plexxikon	2
Oral glucokinase activator (GKA)		
PSN010	OSI	1
R1511	Roche	1
G protein-coupled Receptor(GPR) 119 Agonist		
PSN821	OSI	1
Antisense drug for Glucagon Receptor (GCGR)		
ISIS 325568	Isis	1
Antisense drug for Glucocorticoid Receptor (GCCR)		
ISIS 377131	Isis	Preclinical
Sodium Glucose Transporter 2 (SGLT2) inhibitor		
AVE2268	Sanofi Aventis	2
SAR 7226	Sanofi Aventis	Preclinical
189075	Glaxosmithkline	2
869682	Glaxosmithkline	2
Growth hormone releasing analogue		
TH 9507	Theratechnolgies	1
Nitric oxide (NO) blocking agent		

NOX-700	Medinox	1 staretd in 2002
Antibody		
TRX4	BTG	2
Selective inhibitor of fructose-1, 6-bisphosphatase (FBPase)		
CS-917	Sankyo,Metabasis	2
MB07803	metabasis, Daiichi Sankyo	2
11-beta hydroxysteroid dehydrogenase type 1 (11ß-HSD1) inhibitor		
AMG 221	Amgen, Biovitrum	1
Newer Meglitinides		
Nateglinide with insulin sensitizers	Astellas pharmas	SNDA Filed
Nateglinide with biguanides	Astellas pharmas	SNDA Filed
Islet Regeneration Factors		
DG770 (beta cell regeneration factor)	Develogen AG	3
E1 INT (Islet regeneration)	Transition Therapeutics	2
Miscellaneous		
AMG 837 (Potentiates Glucose Dependent Insulin Secretion)	Amgen	1
MBX 213	Metabolex	1
R 1499	Roche	1
R1438	Roche	2
R1440	Roche	2
PSN 357	OSI	1
NBI 6024	Neurocrine Biosciences	2
MK 0941	Merck	1
MK 1642	Merck	1
Mk 0533	Merck	2
MK0893	Merck	2
Insulins		
Oral Insulin	Emisphere Technologies	2
Technosphere	Mannkind corporation	3
NN344 (Insulin analogue)	Novo Nordisk	1
NN5401(Insulin analogue)	Novo Nordisk	1
iDMS (Insulin Inhalation system)	Novo Nordisk	3
Inhaled insulin	Bristol Meyers Squibb	1
Inhaled insulin	Eli Lilly	2
Exubera (Inhaled insulin)	Pfizer	4
Oal Lyn (Inhaled insulin)	Generex	2
Nasulin	Bentley	2

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