Review Article

Newer Approaches in The Treatment of Diabetes Mellitus

Kamlesh P. Patel¹, Harsh M. Joshi², Falguni D. Majmudar³, Varsha J. Patel⁴

¹Associate Professor; ²4th Year Resident; ³Assistant Professor; ⁴Professor and Head

Department of Pharmacology: Smt. NHL Municipal Medical College, Ahmedabad.

ABSTRACT

Diabetes Mellitus is a public health problem worldwide. The most effective anti-diabetic drugs currently available include insulin and newer insulin preparations, sulphonylureas, biguanides, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, incretins, guar gum and glucomannan. However, the future therapies will need to focus on those patents who do not respond well to these treatments and who account for 50% of the health care costs of Diabetes Mellitus. Drug development for diabetes mellitus has been directed at improving currently available drugs and findings new compounds. In this review article, we will review the role of future new chemical entities able to target the metabolic disorder. Some of these new anti-diabetic treatment strategies may in the future not only control symptoms and modify the natural course of diabetes, but also potentially prevent or cure the disease.

Key Words: Diabetes Mellitus, Metabolic Disorder, Antidiabetics, Incretins

INTRODUCTION

Approximately 186,000 people less than 20 years of age have diabetes. Each year, about 15,000 people less than 20 years of age are diagnosed with type 1 diabetes. Healthcare providers are finding more and more children with Type 2 diabetes, a disease usually diagnosed in adults ≥40 years of age. Children who develop Type 2 diabetes are typically overweight or obese and have a family history of the disease. Most are American Indian, black, Asian, or Hispanic/Latino.

Diabetes mellitus, long considered disease of minor significance to world health, is now taking its places as one of the main threats to human wealth in 21st century. The incidence of the disease in general population by the year 2010 was 210 million, and it is presumed to be increased to 300 million by the year 2025.¹

The current therapies do not cure Diabetes Mellitus completely and hence the symptoms return soon after the treatment is stopped. Therefore, development of novel drugs may allow resolution of these changes. Drug development for Diabetes Mellitus has been directed at improving currently available drugs and findings new compounds.

NEWER APPROACHES

Peroxisome Proliferator Activated Receptors (PPARs):-
Peroxisome proliferator activated receptors (PPARs) are transducer proteins belonging to nuclear receptor super family. Till date, three major types of PPARs, encoded by separate genes have been identified: they are PPARα, PPARβ/δ and PPARγ². Peroxisome - proliferator activated receptor gamma (PPARγ) is a transcription factor activated by thiazolidinediones (TZDs). In transactivation, which is DNA-dependent, PPARγ forms a heterodimer with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results, ultimately in transcription of PPARγ target genes. After ligand binding, PPARs undergo conformational changes, which lead to recruitment of cofactor proteins and coactivators. The coactivators interact with nuclear receptors in a ligand dependent way and influence the set of genes transcribed.

PPAR α/γ Dual Agonist-
These agents are shown to ameliorate the hyperglycemia and hyperlipidemia associated with Type 2 diabetes. In addition to their benefit on lipids, the activation of PPARα may mitigate the weight gain induced by PPARγ activation. So this dual agonist is supposed to provide additive and possibly synergistic effects. First literature report of a balanced PPAR α/γ dual agonist was of KRP-297 (MK-767), a T2D derivative that was reported to bind PPARα and PPARγ. Others are tesaglitazar (AZ-242), ragaglitazar and muraglitazar³.
Glucagon like Peptide-1 (GLP-1) Hormone:
It is the incretin hormone acting via GLP-1 receptor (a G-protein coupled receptor). When blood glucose levels are high this hormone stimulates insulin secretion and biosynthesis and inhibits glucagon release leading to reduced hepatic glucose output. In addition, it serves as an ‘ileal brake’, slowing gastric emptying and reducing appetite. GLP-1 has a number of effects on regulation of β-cell mass: stimulation of replication and growth, inhibition of apoptosis of existing β-cells and neogenesis of new β-cells from precursors. There are two sub-classes of GLP-1 in the phase of clinical development. Exendin-4, a peptide agonist isolated from the venom of lizard and is more potent than natural GLP-1.

β3-Adrenoreceptor Agonist:
β3-Adrenoreceptor agonist showed marked selectivity for stimulation of lipolysis and hence for oxygen and energy consumption in skeletal muscle and adipose tissue. SR- 58611 (Sanofi-Synthelabo) and TAK-677 (Takeda) are some of the compounds in this series undergoing phase II clinical trials. In certain types of fat cells, the β adrenergic receptor (β3AR), which belongs to the superfamily of G-protein coupled receptors (GPCRs), functions in a manner contrary to the general adrenergic system in which activation of β3AR actually induces the waste of metabolic energy. Agonists of this receptor activate the uncoupled protein (UCP) which causes the expenditure of metabolic calories as heat.

α-Lipoic Acid:
α-Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to man. LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for generating glucose metabolism and cellular energy production. LA pretreatment maintains the intracellular level of reduced glutathione (the major intracellular antioxidant) in the presence of oxidative stress, and blocks the activation of serine kinases that could potentially mediate insulin resistance. Thus, one potential explanation for the protective effects of LA might be related to its ability to preserve the intracellular redox balance, thereby blocking the activation of inhibitory stress-sensitive serine kinases including IKKbeta. This stress-sensitive kinase is a crucial regulator of the transcription factor i.e.

necrosis factor-kappaB (NF-kappaB), a major target of hyperglycemia, cytokines, reactive oxygen species, and oxidative stress. LA and other agents that interfere with the persistent activation of the NF-kappaB pathway appear to be promising approaches to increase insulin sensitivity, and perhaps even as treatments for complications of diabetes in which NF-kappaB activation has been implicated.

Liver Selective Glucocorticoid Antagonists
Glucocorticoids raise blood glucose levels by functionally antagonizing the action of insulin, thereby inhibiting glucose disposal and promoting hepatic glucose production and output. So the approaches towards liver selective glucocorticoid antagonist have a potential role in the management of Type II Diabetes Mellitus. Mifepristone has shown glucocorticoid antagonist action and few other similar compounds have been tested in which A-348441 showed reduction in glucose levels and improved lipid profiles in an animal model of diabetes.

Dipeptidyl Peptidase IV Inhibitors:
DPP-IV inhibitors stabilize endogenous GLP-1 and induce insulin secretion in a glucose-dependent manner in contrast to insulin tropic agents which release insulin in glucose independent manners which manifest the hypoglycemia as a residual effect. Thus, the use of DPP-IV inhibitors increases the circulating levels of endogenous GLP-1 leading to increased insulin secretion, biosynthesis and inhibiting glucagon release. Example-saxagliptin, dulogliptine, gemgliptin, alogliptine, linagliptine.

Protein Tyrosine Phosphatase-1b (PTP-1b):
PTP-1B, belongs to non transmembrane class of enzymes. PTP-1B is an abundant enzyme expressed in nearly all tissues. PTP-1B acts as negative regulator of insulin signaling. It acts by causing dephosphorylation of insulin receptor. It also causes negative regulation of insulin signaling. It is involved in Type-2 diabetes & obesity. Administration of PTP-1B antisense oligonucleotides to diabetic obese mice reduces plasma glucose and brings insulin level to normal.
PTP-1B Inhibitors:  
PTP-1B inhibitors are phosphate-based. The most studied phosphate-based PTP-1B inhibitors are difluorophosphonates. 2 (Oxalamino)-benzoic acid (OBA) was identified as a general, reversible and competitive inhibitor of several PTPase using a scintillation proximity recently pyrimidotriazinepiperidine analogues with oral glucose lowering effect in ob/ob mice. Alpha-bromoacetophenone derivatives act as potent PTP inhibitors by covalently alkylation the conserved catalytic cysteine in the PTP active site.7

Glycogen synthase kinase (GSK-3):  
The key enzyme involved in glycogen metabolism, is now known to regulate a wide range of cell functions, its ability to phosphorylate and inhibit glycogen synthase (GS), deactivation of GS and decrease its affinity to allosteric activation by glucose-6-phosphate. In addition, it has been reported that GSK-3 can also phosphorylate insulin receptor substrate. Lithium ion (Li) has been found to cause relatively specific inhibition of GSK-3 and has been reported to have insulin like effects.8,9,10

AMP-Activated Protein Kinase:  
Glucose disposal and insulin resistance in this tissue is one of the earliest contributing factor to the pathogenesis of Type 2 diabetes. AICAR (5-aminoimidazole-4-carboxamide ribonucleoside), metabolized to ZMP which is an analog of AMP - increases muscle glucose uptake concomitantly with glucose transporter 4 (GLUT4) translocation to the plasma membrane 11.

Fructose-1, 6-bisphosphatase as a therapeutic target for Type 2 diabetes:  
The recent discovery and characterization of potent and selective inhibitors of fructose-1,6-bisphosphatase (FBPase) has provided new insights into the therapeutic utility of gluconeogenesis inhibitors the potential of FBPase inhibitors as a new class of antidiabetic drugs and increased endogenous glucose production (EGP). In healthy individuals, gluconeogenesis accounts for 50% of EGP after an overnight fast and increases progressively to account for over 90% of EGP following 40 h of fasting12,13.

EGP is suppressed by a rapid and near complete inhibition of glycogenolysis and slower and more modest inhibition (30–50% within 4 h) of gluconeogenesis. Intracellular F2,6BP levels are controlled by a glucagon-sensitive enzyme, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, MB05032, that inhibits human liver FBPase noncompetitively with an IC50 of 16 nm and shows excellent selectivity for FBPase relatively to other AMP-binding enzymes. CS-917, a prodrug form of MB05032 designed to overcome its cellular penetration and pharmacokinetic limitations, is currently undergoing clinical evaluation14.

Estrogen Receptors: New Players in Diabetes Mellitus:  
Recent data have revealed a surprising role for estradiol in regulating energy metabolism and opened new insights into the role of the two estrogen receptors, ERα to ERβ in this context. New findings on gene modulation by ERα to ERβ of insulin-sensitive tissues indicate that estradiol participates in glucose homeostasis by modulating the expression of genes that are involved in insulin sensitivity and glucose uptake.15

Salsalate:  
It is a non-steroidal anti-inflammatory drug (NSAID). Salsalate belongs to a class of drugs called salicylates. Salsalate may work by inhibiting the production of and release of prostaglandins. It is used for Type-2 diabetes. It also reduces blood sugar in obese adults who don't have diabetes, apparently by making insulin work better.14 Side effects are ringing in the ears, loss of hearing, difficulty in breathing or swallowing, shortness of breath, hoarseness, unexplained weight gain.

Resveratrol:  
In mice and rat experiments, anticancer, anti-inflmmatory, blood sugar-lowering and other beneficial cardiovascular effects of resveratrol have been reported. In humans, however, while reported effects are generally positive, resveratrol may have lesser benefits. Studies have shown resveratrol possesses hypoglycemic and hypolipidemic effects both in streptozotocin (STZ)-induced diabetic rats and STZ-nicotinamide-induced diabetic rats. Resveratrol ameliorates common diabetes symptoms, such as polyphagia, polydipsia, and body weight
loss. Other diabetic animal model studies by different researchers have also demonstrated the antidiabetic effects of resveratrol.

**L-Arginine:**

In recent years it is known that diabetes can affect the heart muscle is independent than through the involvement of early atherosclerotic coronary arteries that cause ischemic heart disease. This is presumably due to changes such as the occurrence of interstitial fibrosis, the formation of collagen and hypertrophy of cardiac muscle cells. For decades, it has been known that nitric oxide is not only a role in the control of vasomotor tone but also play a role in the homeostasis of blood vessels and nerves as well as immunologic processes. Endogenous nitric oxide is produced through changes in the amino acid L-arginine to L-citrulline by the enzyme NO-synthase (NOS). L-arginine is the substrate for the formation of NOS, so it is assumed that L-arginine supplementation may activate NOS and increase NO production and improve vasodilation.

**DiaPep277:**

It is a synthetic peptide of 24 amino acids derived from the sequence of the human heat shock protein 60 (Hsp60). The peptide modulates the immune response that leads to autoimmune diabetes by diminishing or blocking the immunological destruction of beta cells. Treatment of Type 1 diabetes patients with DiaPep277 may have several medical benefits including prevention of disease deterioration, improved glycemic control, reduction of daily insulin dose requirements, and delay or reduction of diabetic complications. Benefit is expected in newly diagnosed adults with Type 1 diabetes, newly diagnosed child or adolescent with Type 1 diabetes.

**Gene therapy:**

Gene therapy, developing rapidly as a result of advances in molecular biology and the Human Genome Project, is now highlighted as a most hopeful technology of the 21st century. The major goal of gene therapy in Diabetes Mellitus (DM) is to maintain euglycemia in face of wide variations in dietary intake. Although some obstacles remain to be overcome, the risk-benefit ratio of gene therapy in DM is better than that of lifelong injections of insulin, and islet transplantation, which faces the problems of donor shortage and rejection. This review focuses on the recent advances in gene therapy of insulin-requiring diabetes, with particular emphasis on 1. The gene delivery systems by viral vectors, since most gene therapy approaches for DM involve the use of viral vectors, paying special attention to current efforts to overcome the disadvantages of adenovirus, adenovirus-associated virus and retrovirus vectors and targeting gene delivery for optimal efficiency of gene expression: Coupling the synthesis and release of the transgene insulin to serum glucose concentrations, especially with reference to the current promoters controlling at transcriptional level the ectopic insulin expression in autologous hepatocytes; beta-cell replacement strategies: engineering of beta-cells, especially those derived from pluripotent stem cells, non beta-cells, and on a new corner, the K cells.

**Recombinant Human Glutamic Acid-rhGAD65:**

Type I diabetes results from autoimmune destruction of islet β cells. In the NOD (non-obese diabetic) mouse model, this β cell injury is thought to involve autoantigen-specific CD4 T cells with a Th1 phenotype and specific CD8 T lymphocytes. Diabetogenic CD4 T cell clones usually produce Th1 cytokines and many Th1 cells derived from islet infiltration of NOD mice and reactive to insulin can transfer diabetes. Very recently, DNA vaccination encoding GAD65, insulin or HSP70 has been shown to be an effective approach to prevent Type I diabetes in the NOD mice. Such therapeutic trials tested in the mice are considered as future possible specific immune therapy of type I diabetes in humans.

**Anakinra:**

In a recent clinical trial, the arthritis drug Kineret (anakinra) helped to control blood glucose levels in diabetes. The drug is known as a recombinant human interleukin-1-receptor antagonist. Kineret blocks the production of interleukin-1, which is a type of cytokine associated with joint inflammation. In diabetes, interleukin-1beta is produced in the pancreas. High glucose levels appear to trigger the release of interleukin-1beta. This not only reduces the function of beta cells in the pancreas, but can cause beta cells to self-destruct.
Otelixizumab:

Otelixizumab is one of the several investigational monoclonal antibodies that target CD3, a T-lymphocyte receptor involved in normal cell signaling. More specifically, otelixizumab targets the epsilon chain of CD3. Data suggest that the drug works by blocking the function of effector T-cells, which mistakenly attack and destroy insulin-producing beta cells while stimulating regulatory T-cells, which are understood to protect against effector T-cell damage, thus preserving the beta cells' normal ability to make insulin. 25

The efficacy and safety of otelixizumab for the treatment of autoimmune Type 1 diabetes is currently being studied in a pivotal Phase 3 study called DEFEND (Durable-response therapy Evaluation For Early or New-onset type 1 Diabetes), which has been completed in August 2012. 26

Teplizumab:

Teplizumab is a monoclonal antibody which is used as an immunosuppressive drug. It is a humanized Fc-engineered monoclonal antibody also known as MGA031 and hOKT3y1 27 It targets at protecting the remaining beta cells in newly diagnosed T1 diabetics. It has been used experimentally in Type 1 Diabetes Mellitus, but these agents [i.e. anti-CD3 antibodies] alone do not restore normal glucose control. They must be combined with other anti-diabetic drugs.

Stem cell therapy:

Type 1 diabetes is caused by the body's own immune system attacking its pancreatic islet beta cells and requires daily injections of insulin to regulate the patient's blood glucose levels. A new method uses stem cells from chord blood to re-educate a diabetic's own T cells and consequently restart pancreatic function reducing the need for insulin. Stem Cell Educator therapy slowly passes lymphocytes separated from a patient's blood over immobilized chord blood stem cells (CBSC) from healthy donors. After two to three hours in the device the re-educated lymphocytes are returned to the patient. The progress of the patients was checked at 4, 12, 24 and 40 weeks after therapy. 28

CONCLUSION

Newer approaches mentioned in this article have been directed at improving currently available anti-diabetic drugs and finding the new compounds. The role of future new chemical entities will be to target the metabolic disorder through multi-facet mechanisms. Some of these new anti-diabetic treatment strategies may in the future not only control symptoms and modify the natural course of diabetes, but also potentially prevent or cure the disease.

ACKNOWLEDGEMENT

The authors are thankful and acknowledge the support given by Dr. Pankaj R. Patel, Dean, and Dr. Varsha J. Patel, Professor and Head, Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad for this study.

REFERENCES

Handal R.S., Mechanism by which metformin reduces glucose production in Type 2 Diabetes. Diabetes, 2000; 49: 2063-2069.


Aspirin cousin could help prevent diabetes. blogs.wsj.com


Yong Zhao, Zhaoshun Jiang, Tingbao Zhao, Mingliang Ye et al., Reversal of type 1 diabetes via islet beta cell regeneration following immune modulation by cord blood-derived multi-potent stem cells. BMC Medicine.