ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

A REVIEW ON: MULTIPLE THERAPEUTIC TARGETS ON THE MANAGEMENTS OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is diseases which reduces the blood sugar (glucose). Glucose is essential to your health because it is source of energy for the cells that make up your muscles and tissues. It is act as a source of fuel.Diabetes Mellitus is also known to be a chronic metabolic disorder (3rd Killer of human). It is corresponding with several pathophysiological states like hypertension & hyperlipidemia. It is characterized by high fasting and post-prandial glucose level in blood stream. There are numerous cellular and metabolic targets drawn to enhance by many ways like increase in pancreatic function through anti-inflammation, reducing carbohydrate metabolism, increase in insulin secretion, also boost the activity of insulin on its target protein. So here we studied number of targets which will potentially increase the insulin secretion by binding with proper ligand molecule.

Keywords*:* - Diabetes Mellitus, Targets, Insulin secretion, Ligand Molecule

INTRODUCTION

Diabetes mellitus is a form of metabolic disorder where blood glucose level in the blood stream raises high, because of lack of insulin. It is generally observed in middle age people and the children in most developed countries. Diabetic patients develop complications like obesity, stroke and heart failure. Diabetes mellitus is also known to be a chronic metabolic disorder (3rd Killer). It is correlated with several pathophysiological states like hypertension and hyperlipidemia. It is characterized by high fasting and post-prandial glucose level in blood stream. It is mainly classified into three classes: 1. Type I diabetes, 2. Type II diabetes, 3. Gestational diabetes. Type I diabetes is also known as insulin dependent were β-cells are absent or completely non-functional (Autoimmune disease). Type II diabetes is insulin independent where β-cells are functional can be cured by giving OHA (sulfonyl ureas or biguanides).

VARIOUS TARGETS OF DIABETES MELLITUS

DM is the decrease in carbohydrates metabolism which results in rise in blood glucose level. Long term disclosure to DM can cause the failure or low function of various organs includes kidneys, heart, eyes, etc.[1]

As per INDIAB estimation, the current status of DM there is 72.96 million cases of diabetes in adults. In urban areas it ranges between 10.9-14.2% & in rural area it is between 3-7.8%.[2,3] It is mostly among the population aged 20 years and among the individuals between 50 years. The reason behind the global pandemic is aging population, decrease in physical activity in people, urbanization.

There are numerous cellular and metabolic targets drawn to enhance by many ways like rise in pancreatic function through anti-inflammation, increase in insulin secretion, also boost the action of insulin on its target protein.[3]

There are many targets against diabetes include:

1. α-Glucosidase inhibitors[5]
2. AMPK (AMP-activated protein kinase)[6]
3. Dapagliflozin[7]
4. FFAR2 (Free fatty acid receptor 2)[8]
5. IRS 2 (Insulin receptor substrate 2)[9,10]
6. MAPK (mitogen-activated protein kinase)[11]
7. PTP1B (Protein tyrosine phosphatase 1B)[12,13]
8. SGLTs (Sodium–glucose co-transporters)[14]

9. CXCR1/2 (chemokine receptor)[15]

α- Glucosidase Inhibitors:-

To cure diabetes we can use α-glucosidase inhibitors which help in reducing the blood glucose level. If we use 1,2-benzothiazine 1,1-dioxide derivatives as a potent α-glucosidase inhibitors by using in silico screenings, then the α-Glucosidase inhibitors which may stop/reduce carbohydrate metabolism &regain the postprandial hyperglycemia so it is useful tool in diabetes.

The common α-glucosidase inhibitors (AGI) are voglibose, miglitol and acrabose which can be useful in PP hyperglycemia. But many of AGIs of α-glucoside linkage have some disadvantages like gastrointestinal problem, some contain many sugar moieties and some have multistep synthesis. Hence, we have to find a drug molecule with adequate anti-α-glucosidase activity and nearly no side effects.[16]

1,2-benzothiazine 1,1-dioxides it is class of organic compounds in heterocyclic chemistry. 1,2-benzothiazine 1,1-dioxides have many potential activities like anti-HIV, anti-cancer, cholinesterase inhibitors, anti-viral, anti-inflammatory etc.principle mechanism of α-glucosidase inhibitors shows in Figure no 1.

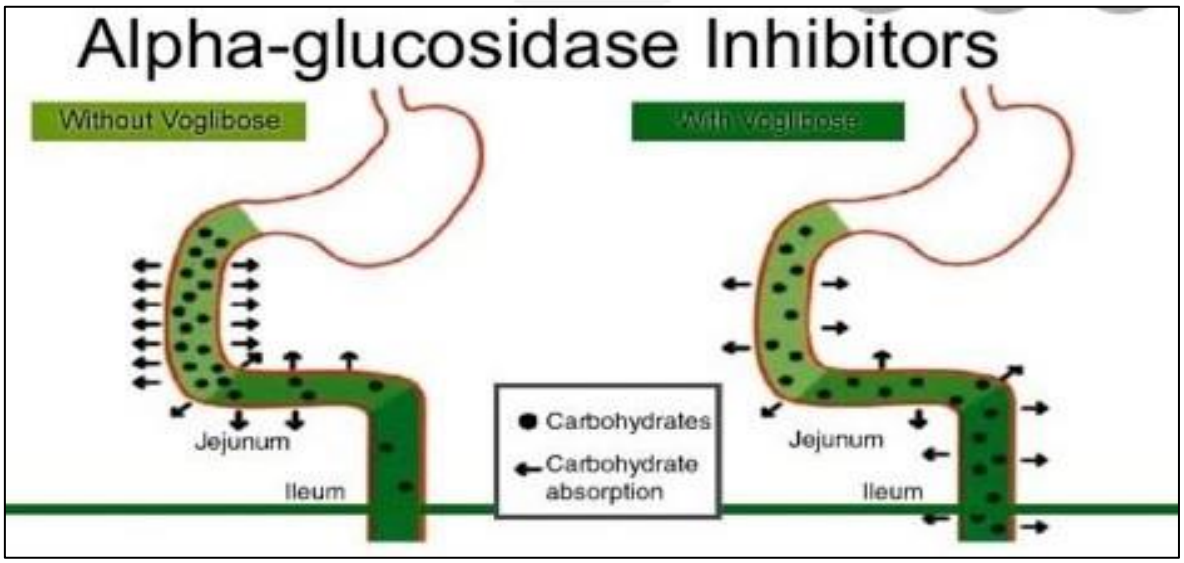

Figure 1:α-glucosidase inhibitors (AGI)

AMPK (AMP-activated protein kinase):-

AMP-activated protein kinase (AMPK) it is an enzyme which is called a master regulator of metabolism. It is activated whencellular energy level is minimum/low i.e. intracellular AMP: ATP ratio is high. After activation, AMPK signals through its downstream substrates which

bring back normal energy levels by stimulating processes that ATP like fatty acid. Then they inhibit those which use ATP like protein synthesis. So after AMPK activation it improves the insulin sensitivity & glucose uptake.

It exists in a heterotrimer form. It consists of α-subunit, β- and γ-subunits(regulatory). Each subunit has distinct isoforms namely α1, α2, β1, β2, γ1, γ2, γ3 with total of 12 possible heterotrimer combinations. The practical difference between the various isoforms is unclear. Some are tissue-specific & some are located in brain, heart, and skeletal muscles.[17,18]

Dapagliflozin:-

The various drugs like metformin may cause gastrointestinal effects includes diarrhoea and nausea, lactic acidosis, sometimes insulin or OHA can cause hypoglycemia, also weight gain. After carried this investigation so far dapogliflozin a sodium-glucose co-transporter-2 (SGLT2) inhibitors has found to new dimensions not for the mechanism of diabetes, but for potential therapeutic activity.

If we study historically the glucosuria is the glucose excretion in the urine which we can said to be a metabolic deteriorate and has so many adverse effects and consequence in history of diabetes. SGLT2 inhibitors mainly target the renal power of glucose which would expect to treat hyperglycaemia.[19]So dapagliflozin is a potential novel drug used in treatment of diabetes. By decreasing renal glucose reabsorption because of enhancing urinary glucose excretion, SGLT2 inhibitors reduce the hyperglycaemia which increases insulin secretion.

FFAR2 (Free fatty acid receptor 2):-

Short-chain fatty acids (SCFAs) are the fatty acids with aliphatic groups of less than six carbons, which are derived from the process of fermentation of dietary fibers &carbohydrates in intestinal tract. They are also a good source of nutrient in humans. The SCFAs are the class of signalling molecules in metabolic process and also in inflammation.

In 2003, there are no of receptors of SCFAs were identified namely GPCRs (G-protein coupled receptor), FFAR2 (Free fatty acid receptor 2), FFAR3 (Free fatty acid receptor 3). FFAR2 appearance is increased in peripheral blood mononuclear cells (PBMCs) from recent advance T1D patients.[20] PBMCs are the cells in blood with round shaped nuclei which also include monocytes and lymphocytes, and they are the most critical components of the immune system in autoimmune disease. The agonist of FFAR2 is phenylacetamide 1 (PA1), which improves the glucose tolerance. Figure no. 2 shows mechanism of free fatty acid receptor 2.

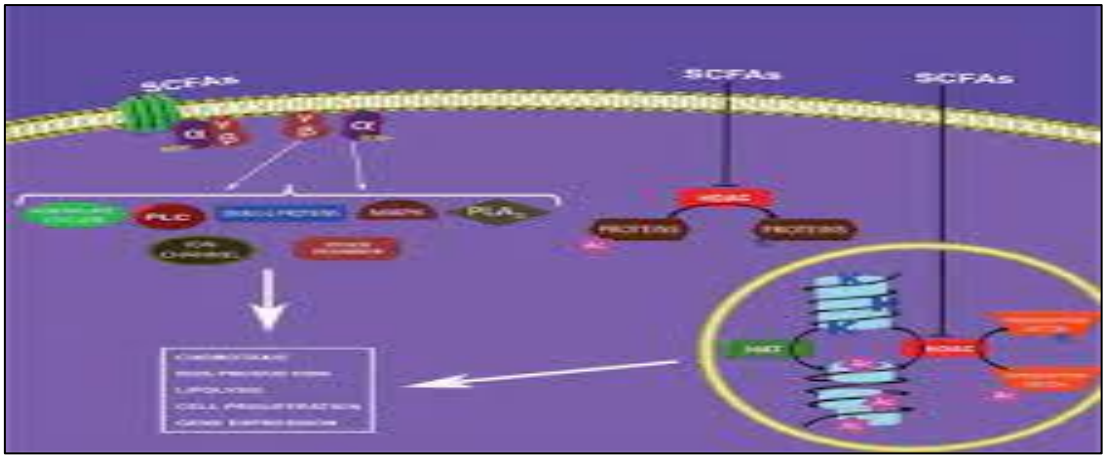

Figure 2: Free fatty acid receptor 2

IRS 2 (Insulin receptor substrate 2):-

Insulin is a key factor for balancing of metabolism in cells mainly, liver, muscle, and adipose cells. The potentiality of insulin to increase glucose transport into muscle &fatty cells is arbitrated by the translocation of a glucose transporter (GLUT4), from intracellular vesicles to cell surface. The fundamental mechanism of insulin is binding to specific cell surface receptors which bring auto phosphorylation and the activation of an intrinsic tyrosine kinase corresponds with the β- subunit.

IRS proteins (IRS-1 and IRS-2) are substratum for the insulin. IRS proteins act as affiliate among activated receptors and signalling proteins with (SH2 Src homology) domains. After insulin inducement, IRS-1 accompanying with some proteins include: phosphatidylinositol (PI-3) kinase. PI-3-kinase it is heterodimeric enzyme which consist of 85-kDa (regulatory subunit) with SH2 domains which is able to bind with tyrosine phosphorylated IRS-1 and another is 110-kDa (catalytic subunit) in which the phosphorylates the inositol ring of PI and its phosphorylated derivatives.[21,22]

PI 3-kinase has been incriminating as the important signal transducers in insulin-stimulated glucose uptake&GLUT4 translocation. So the main role of IRS proteins in the management of PI 3-kinase binding and it activates the insulin-resistant state in human body.

MAPK (mitogen-activated protein kinase):-

Inflammation &cellular dysfunction are the main features of diabetes and diabetic nephropathy. They are correlated with intracellular activation of mitogen-activated protein kinase (MAPK) signalling pathways. The constituent of the DM, which includes hyperglycaemia,

hyperlipidaemia,AGE, angiotensin II[23] which stimulate increased MAPK signalling in cells and build up tissue injury.

p38 MAPK signalling is recognized to build up inflammatory and profibrotic responses and then they has been connected with other cellular functions like glucose uptake and proliferation Levels of activated p38 suggest that the responses is prime most for the pathogenesis of diabetes and also its complications.

After activation of p38 amplify production of monocyte chemoattractant protein-1 (MCP-1) by vascular endothelial cells, induces angiotensinogen production tubular cells, stimulates TGFβ-induced fibronectin aggregation in renal interstitial fibroblasts.

PTP1B (Protein tyrosine phosphatase 1B):

In current situation, so many options to cure type 2 diabetes by doing exercise and by taking dietary supplements for obesity and to improve insulin sensitivity also for increasing insulin secretion, and to inhibit rate of glucose absorption from the guts.

Till date, Type II diabetes includes medication like biguanides, sulfonylureas, a-glucosidase inhibitors and thiazolidinediones (TZDs). But there are so many drawbacks in their clinical use, CZ these drugs are designed to cure the symptoms not the disease target. So there is necessity for the managing of diabetes and related disorders.

It is a important tool in the negative regulation of insulin signal transduction pathway. And it gives a novel therapeutic strategy for the cure of type 2 DM.[24] PTP1B inhibitors intensify the sensitivity of insulin receptor (IR) and have ability to cure insulin resistance-related diseases. A huge number of PTP1B inhibitors were synthesized and also isolated to check the capacity to restore the insulin signalling.

After all the evidences it indicates that PTP1B inhibitors will increase the altitude of phosphorylation of insulin receptor. And the substrates of PTP1B will promote glucose transporters translocation and also glucose uptake in insulin-sensitive cells.

SGLTs (Sodium–glucose co-transporters):-

Sodium-glucose co-transporters (SGLTs) are mainlyliable for the renal glucose reabsorption, were SGLT2 will perform especially the task while SGLT1will do only remaining. The past ofinhibitors targeting against SGLTs was phlorizin which is found experimentally, which was isolated in the 1800s and which improve the blood glucose level in laboratory animals.

Cell membranes composed of lipids, are impermeable to glucose which is a polar compound. So the convey of glucose requires carrier protein to cross the membrane which is present in cell membrane. After glucose filtratiopn by glomeruli of kidney it is reabsorbed by SGLTs

which being in the epithelial cells of proximal tuble in apical or lumial membrane which transport sodium with that of glucose.

SGLT2 and SGLT1 mainly transport glucose across the proximal convoluted tubule (PCT) cells of kidney with varying capacities as shown in fig.1.1. SGLT2 is high-capacity &low-affinity transporter mainly present in S1 segment of the PCT8. SGLT2 shows around 90% of reabsorption of glucose andSGLT1 with low-capacity &high-affinity transporter with distal S2/S3 segment of the PCT& reabsorb the remaining filtered glucose.[25] SGLT2 catalyses the active transportation of glucose against a concentration gradient across the apical (luminal) membrane by coupling it with the carriage of sodium.

Table 1:- A comparison of characteristics of SGLT1 & SGLT2

	SGLT1	**SGLT2**
Site	Mostly small intestine, some in kidney & heart	Almost exclusively kidney
Renal location	Late proximal straight tubule (S3 segment)	Early proximal convoluted tubule (S1 segment)
Affinity for glucose	High (K_m = 0.4 mM)	Low (k_m = 2mM)
Capacity for glucose transport	Low	High
Percent of renal glucose reabsorption	~10%	~90%

CXCR1/2 (chemokine receptor):-

There are so many substances have which were useful in T1D therapy as single agent, but they give limited success after clinical practice because they target only one or specific immune process. They include molecules that deplete T effector cells which are sometimes administered when T cell response reaches its peak i.e.anti-CD3 & anti-CD2 to stop the β cell damage

The pro-inflammatory interleukin 8 also called as IL-8 is member of CXC chemokine family with about 75 amino acids in chain. In human body there are two-affinity receptor for IL-8 called as CXCR1-8R-A) &CXCR2 (IL-8R-B).[26]

In Type 1 DM & in any other disorders the neutrophils plays an active role in tissue damage. The therapeutic potential of targeting CXCR1 & 2 was examined in which considering a nature of CXC chemokine signalling. The more effective strategy is to target the CXCR1 or CXCR2 receptor.

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