REVIEW ON RECENT ANTIDIABETIC DRUG TARGETED PROTEINS FOR RATIONAL DRUG DISCOVERY AND DEVELOPMENT

INTRODUCTION

Diabetes mellitus refers to a group of disorders with different etiologies. It is characterized by derangements in carbohydrates, proteins and fat metabolism caused by the complete or relative insufficiency of insulin secretion and/or insulin action. This leads to increasing demand for natural or synthetic products with antidiabetic activity with fewer side effects. Computational methods which has emerged as very useful and money saving tool in drug design, can be effectively employed in designing multiple receptor activating ligands. The design of multiple receptor activating ligands is very challenging as it requires structural fine tuning so that the designed molecule should bind to and activate the targeted receptors of structural similarity. In this review article, we made an attempt to list out all emerging drug targets of type 2 diabetes. The aim of our work is to provide antidiabetic drug target related information so as to enable the computational chemists to strategically develop effective drugs in antidiabetic drug discovery and development [1-19].

ABSTRACT

Diabetes mellitus (DM), often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. The aim of this article is to list out some common potential protein drug targets involved in type 2 diabetes, gaining novel initiative to design new drug candidate to generate antidiabetic drugs against type 2 diabetes.

Key words: Diabetes mellitus (DM), Antidiabetic drug targets

ALDOSE REDUCTASE (ALR)

Aldose reductase (EC 1.1.1.21, ALR), a member of the aldo-keto reductase superfamily, is the first and rate-limiting enzyme of the polyol pathway. It catalyzes the NADPH-dependent reduction of glucose to sorbitol which, in some tissues, is oxidized to fructose by sorbitol dehydrogenase. Under euglycaemic conditions, ALR, which has low affinity for glucose, produces little sorbitol. Indeed, a wide variety of aldehydes, especially medium-chain hydrophobic lipid-derived aldehydes and their glutathione adducts, are reduced more efficiently than glucose by ALR. This would suggest that the most common role of ALR may be the removal of potentially toxic aldehydes generated during lipid peroxidation. In contrast, under hyperglycaemic conditions, an excess of glucose (more than 30% of the total metabolized amount) is converted to sorbitol through the polyol pathway in tissues possessing insulin-independent uptake of glucose, leading to intracellular accumulation of this osmotically active polyol. At the same time, NADPH and NAD+ deprivation causes changes in cellular redox potentials, increased oxidative stress and reduced activity of other NADPH-dependent enzymes, such as nitric oxide (NO) synthase and glutathione reductase. Alterations of cytokine signalling and kinase cascades are also involved. These metabolic and biochemical changes result in inflammation, chronic vascular damage and decrease in
GLUCOKINASE (GK)

Glucokinase (GK or GLK, also known as hexokinase IV or hexokinase D (ATP: D-glucose-6-phosphotransferase, EC 2.7.1.2)), is a 50-kDa cytoplasmic enzyme and one of the four hexokinases found in mammals that catalyze the conversion of glucose to glucose-6-phosphate (G-6-P), the first step of glucose metabolism. In addition to neuronal/neuroendocrine cells GK is selectively expressed in pancreatic β-cells and liver parenchymal cells (hepatocytes), both of which are known to play crucial roles in whole-body blood glucose homeostasis. Activators of glucokinase increase the sensitivity of the enzyme to glucose, leading to increased insulin secretion and liver glycogen synthesis and a decrease in liver glucose output. Thus, small molecule glucokinase activators have been demonstrated to be effective glucose-lowering agents in animal models of type 2 diabetes and have advanced into clinical studies [28-37].

FRUCTOSE 1,6- BISPHOSPHATASE (FBP)

Fructose-1,6-bisphosphatase (FBP) has long been recognized as a potential therapeutic target for the treatment of type 2 diabetes mellitus (T2DM). As a rate-limiting enzyme of the gluconeogenesis (GNG) pathway, it catalyzes the hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate. Thus, the inhibition of gluconeogenesis is a useful approach in reducing increased blood glucose levels in patients with type 2 diabetes. FBP inhibitors would lower blood glucose levels by reducing hepatic glucose output and are expected to be a novel class of drugs for the treatment of type 2 diabetes [38-42].

α-GLUCOSIDASE (AG)

Glucosidases are responsible for the catalytic cleavage of a glycosidic bond in the digestive process of carbohydrates with specificity depending on the number of monosaccharides, the position of cleavage site, and the configuration of the hydroxyl groups in the substrate. The α- and β-glucosidases are most extensively studied and are known to catalyze the hydrolysis of the glycosidic bonds involving a terminal glucose at the cleavage site. Of the two popular glucosidases, α-glucosidase (EC 3.2.1.20) has drawn a special interest of the pharmaceutical research community because it was shown that the inhibition of its catalytic activity led to the retardation of glucose absorption and the decrease in postprandial blood glucose level. This indicates that effective α-glucosidase inhibitors may serve as chemotherapeutic agents for clinic use in the treatment of diabetes and obesity. The catalytic role in digesting carbohydrate substrates also makes α-glucosidase a therapeutic target for the other carbohydrate-mediated diseases including cancer, viral infections, and hepatitis [43-51].

GLYCOGEN PHOSPHORYLASE (GP)

Glycogen phosphorylase, the rate determining enzyme of glycogen degradation, catalyzes the breakdown of glycogen to glucose--phosphate. In the liver glucose--phosphate is metabolized further to glucose, which is then secreted into the bloodstream. GP exists in two interconvertible forms, GPa (the phosphorylated form, high activity, high substrate affinity, predominantly R state) and GPb (the nonphosphorylated form, low activity, low substrate affinity, predominantly T state). So inhibition of GPa may represent another useful therapy for the treatment of Type 2 diabetes [52-56].

DIPEPTIDYL PEPTIDASE IV (DPP IV)

Dipeptidyl peptidase IV (EC 3.4.14.5) is an important drug target for type 2 diabetes. The major function of DPPIV is to degrade incretins including glucagon-like peptide (GLP-) and glucose-dependent insulinotropic polypeptide (GIP), which regulate insulin in a strictly glucose-dependent manner. Inhibition of DPP-IV prolongs the in vivo half-life of these incretins, leading to the proposal that the DPP-IV inhibitors could enhance insulin secretion and improve glucose tolerance, making them valuable for treating type-2 diabetes. DPP-IV is a serine protease that specifically cleaves N-terminal dipeptides from polypeptides with Pro and Ala at the penultimate position. Most DPP-IV inhibitors were designed according to the substrate P1 site structure (occupied by proline), namely the proline-like compounds. The majorities of these are peptide-like compounds and contain cyanopyrrolidine moiety, which forms covalent bond to the catalytic residue Ser630 by the nitrile group. In addition to the proline-like compounds, a variety of non-peptide-like and reversible DPP-IV inhibitors were also discovered via high-throughput screens and offered new recognition motifs to DPP-IV. Several inhibitors are currently in clinical trials and the first DPP-IV inhibitor Januvia (sitagliptin), was approved by the FDA (U.S. Food and Drug Administration) as a drug for the treatment of type-2 diabetes [57-69].

GLYCOGEN SYNTHASE KINASE-3β (GSK-3β)

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase which was first discovered for its role in phosphorylation mediated deactivation of glycogen synthase, the rate-limiting enzyme in glycogen biosynthesis. Subsequently, GSK-3 has been found to be ubiquitously distributed throughout the body and to play a central role in many cellular and physiological events, including Wnt and Hedgehog signaling, transcription,
insulin action, neuronal function and many others. As a result, inhibition of GSK-3 has emerged as a potential therapeutic approach for a number of pathologies including type 2 diabetes, bipolar disorders and Alzheimer’s disease. GSK-3 exists in two forms, α and β, which share 85% homology (95% in the catalytic domain), but which have shown distinct pharmacology. GSK-3β phosphorylates proteins such as glycogen synthase, acetyl CoA carboxylase, β-catenin, cyclin D1, Tau, etc. which plays a significant role in the signaling pathways. It controls several cellular processes such as differentiation, proliferation, metabolic processes, apoptosis, inflammation, neuronal function, etc. The small molecule inhibitors of GSK-3β have a therapeutic potential for the treatment of human diseases like neurodegenerative diseases, type II diabetes and cancer [70-78].

PPAR-ALPHA (PPARα)

The peroxisome proliferators-activated receptors (PPARs) comprise one of the most important subfamilies of nuclear receptor superfamilies, which functions as ligand-activated transcription factors regulating the expression of target genes. To date, three subtypes of PPAR (α, γ, and β/δ) have been identified. PPAR-alpha is predominantly expressed in the liver and to a lesser extent in variety of cell types, including smooth muscle cells, endothelial cells, and macrophages, playing a pivotal role in atherosclerosis and inflammation process. The role of PPAR-alpha in the regulation of hepatic lipid metabolism was revealed by its association with well known natural fatty acids and the fibrate class of hypolipidemic drugs (fenofibrate, gemfibrozil, and bezafibrate). Activated PPARs get heterodimerized with the 9-cis-retinoic acid receptor (RXR). The heterodimeric receptor complex binds to peroxisome proliferator response elements (PPREs) located in the promoter regions of the target genes (acyl-CoA oxidase (AOX), liver-fatty acid-binding protein (L-FABP), apolipoprotein C-III (apo C-III), and lipoprotein lipase (LPL)), which controls lipid and glucose metabolism. In addition, it has been reported that activated PPAR-alpha produce insulin sensitizing effects to improve glucose tolerance in type II diabetes [79-81].

PPAR-GAMMA (PPARγ)

PPARγ is one of three known PPAR isoforms (α, δ, and γ). A great deal of literature focuses on increasing insulin sensitivity by controlling PPARγ interactions and altering gene expression of various transcription factors. PPARγ is a component of an extensive group of controls for adipogenesis and glucose homeostasis, and both of these processes directly affect obesity and type 2 diabetes. PPARγ is located in high concentrations in adipocytes, and has also been found in significant amounts in the retina, cells of the immune system, and colonic epithelial cells. Functionally, PPARγ down regulates the expression of pro-inflammatory cytokines by antagonizing the activities of transcription factors such as AP- and NF-κB, and favoring the nucleocytoplasmic shuttling of the activated p65 subunit of NF-κB. As a consequence of the important roles PPARs play in controlling metabolic homeostasis and inflammatory processes, they are all well recognized as molecular targets for drugs against metabolic diseases, such as type 2 diabetes, and treatment of immuno-inflammatory disorders [82-86].

PROTEIN TYROSINE PHOSPHATASES 1B (PTP 1B)

Protein tyrosine phosphatases (PTPs) are enzymes that can catalyze the removal of phosphate groups from phosphotyrosyl residue in proteins. In conjunction with protein tyrosine kinases (PTKs), they are responsible for the regulation of a wide variety of important cellular processes, such as T-cell activations, cell growth and proliferation, and oncogenic activation. PTP 1B, the first purified PTP, is an intracellular non-receptor PTPs. It plays a major role in the dephosphorylation of insulin receptor in many cellular and biochemical studies. A study with PTP 1B knockout mice has demonstrated that loss of PTP 1B activity resulted in an enhancement of insulin sensitivity and resistance to weight gain, so potent PTP 1B inhibitors may be potential pharmacological agents for the treatment of type 2 diabetes and obesity [87-92].

REFERENCES

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