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COMPUTATIONAL APPROACHES FOR ALDOSE REDUCTASE: A KEY THERAPEUTIC TARGET IN DIABETES MANAGEMENT AND THE ROLE OF INNOVATIVE INHIBITORS

Asmath Maziyuna Fabin

Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Seethangoli, Bela, Kasaragod, Kerala, 671321

ABSTRACT :

Diabetes mellitus is a clinical condition. It involves altered physiological glucose levels and can lead to long-term complications. These complications include: nephropathy retinopathy neuropathy, cataracts and cardiovascular disorders. Aldose reductase is an enzyme from the aldo-keto reductase superfamily. It has an important role in polyol pathway. This pathway catalyses conversion of glucose into sorbitol. Inhibitors of aldose reductase have gained attention. They are considered as a therapeutic target for mitigating diabetes mellitus-related complications.

Reducing sorbitol flux through polyol pathway is strategy for addressing diabetes. This is done using aldose reductase inhibitors. The review presented here provides an overview of aldose reductase's role in diabetic complications. It discusses advances made in the development of these inhibitors.

Various computational approaches have been used for targeting aldose reductase. This is especially done against diabetes mellitus. ARIs act as strategy for managing both diabetic and non-diabetic complications. Through this, it provides pathway for new therapeutic solutions.

INTRODUCTION :

Molecular docking is potent in silico drug design. It's an approach. This approach aids in predicting possible binding sites. It predicts these for a ligand in target protein. A virtual screening technique is implemented for effective selection. Large libraries of compounds are streamlined to a subset. High binding affinities to the target protein's receptors is the goal.The docking process involves computational identification. It identifies the optimal ligand conformation. This process occurs within binding pocket site of the target protein. The energy of the complex is minimized. This enhances binding interactions. Aldose reductase is a rate-limiting enzyme in the polyol pathway. Glucose is metabolized through the hexokinase pathway under normal conditions. During hyperglycemia, however, the hexokinase pathway is saturated with excess glucose. This activates aldose reductase. It then converts glucose into sorbitol or other sugar alcohols.Accumulation of sorbitol indirectly contributes to diabetic complications. These include diabetic nephropathy and retinopathy. Alrestatin was a drug withdrawn during clinical trials. The reason was various side effects like fever and nausea. There was also diarrhea and liver enzyme elevation. Skin reactions like Stevens–Johnson syndrome were also common. Last but not the least, hepatic necrosis was also observed. This was particularly related to the drug tolrestat.Diabetes has reached alarming proportions worldwide. WHO reported a rise in cases. It went from 108 million to 422 million from 1980 to 2016. This surge has greatly increased both mortality and morbidity. As a result there is an urgent need for new therapeutic strategies. This work brings to light the development of targeted drug discovery approaches. These are meant for aldose reductase inhibitors. Existing drugs have some drawbacks. Such issues need to be addressed. Using molecular docking, is a step towards this. The aim of this study is to improve diabetes management. It also seeks to mitigate related complications.

ALDOSE REDUCTASE :

Study of Aldose reductase (AR)

Aldose Reductase (AR) (EC 1.1.1.21 AKR1B1 and ALD2) is an enzyme. It belongs to aldo-keto reductase superfamily. It catalyzes rate-limiting step in polyol pathway of glucose metabolism. AR is a 36 kDa cytoplasmic protein. It has a triose phosphate isomerase structural motif. This motif includes 10 peripheral α-helices. These encircle an inner β-pleated sheet barrel. The structure consists of 315 amino acid residues.

Cofactor NADPH is positioned at top of the β/α barrel. Nicotinamide ring extends into center barrel. Pyrophosphate group is at the lip of the barrel. AR lacks structural carbohydrates lipids, metal ions. The catalytic active site is housed within barrel. This site is composed of hydrophobic residues and an "anion well." The nicotinamide ring of NADPH or NADP+ is included. Critical residues Tyr48 and His110 are also included. AR is a small monomeric protein. It is primarily known for reducing glucose to sorbitol. This reduction is initial step of the polyol pathway.AR uses NADPH to facilitate the reaction. This occurs during conversion of an aldehyde substrate to an alcohol. The reduction step is transfer of the pro-R-hydride (H) from the C4

carbon of NADPH nicotinamide ring. It gets transferred to the re-face of substrate's planar carbonyl group. Simultaneously a proton is transferred from Tyr48, via His110, to the substrate. The reaction product is subsequently released. A conformational change enables this release. This conformational change enables the dissociation of the oxidized nucleotide, NADP+.

Role of AR in Diabetic Complications (Polyol Pathway)

A key player in the polyol cascade, aldose reductase (AR) becomes more active in hyperglycemic circumstances linked to diabetes. AR uses NADPH as a cofactor to catalyze the conversion of glucose to sorbitol. Normally a minor mechanism for glucose metabolism, increased glucose flux into the polyol pathway in diabetic conditions causes a number of severe effects, including:

- NADPH Depletion: AR consumes too much NADPH. It decreases its availability for other essential cellular functions. One such function is the regeneration of glutathione. This reduction negatively impacts the antioxidant capacity of cell. It results in oxidative stress.
- Sorbitol Accumulation : Sorbitol dehydrogenase converts sorbitol to fructose gradually. But in high-glucose conditions sorbitol accumulates. This causes osmotic stress. It can damage tissues. Tissues such as nerves, eyes and kidneys are particularly vulnerable.
- The Problem of Oxidative Stress: One of main culprits behind diabetes problems is oxidative stress. This stress worsens because of decrease in NADPH. There is an increase in reactive oxygen species or ROS.
- Effects Specific to Tissue: Sorbitol build-up in nerve cells disrupts their normal function. It is a factor in causing diabetic neuropathy. AR activation in retinal cells triggers inflammation. It also causes oxidative stress. This leads to a condition known as diabetic retinopathy. AR-mediated processes facilitate diabetic nephropathy. They cause glomerular dysfunction. They also lead to structural damage in the kidneys.

Because it plays a role in polyol pathway AR becomes major mediator. This is in pathophysiology of diabetic issues in general. It can be a promising therapeutic target. The goal can be to reduce these complications. This only scratches the surface of what AR does in the polyol pathway.

COMPUTATIONAL STUDIES WITH ALDOSE REDUCTASE :

D. JAYABAL AND ET AI conducted a study investigating the molecular geometries of diabetic inflammatory cells and the binding affinities of hyaluronic acid conjugates to such target proteins. Using in silico molecular docking, a set of 48 anti-diabetic drugs were screened against the aldose reductase binding pocket 3 protein target. The results showed that, of the 48 drugs selected, three—metformin (CID:4091), phenformin (CID:8249), and sitagliptin (CID:4,369,359)—had a significant binding affinity. Additionally, these three anti-diabetic compounds were conjugated with hyaluronic acid (HA), and their molecular geometry and binding affinity towards the enzyme aldose reductase were evaluated in comparison to the drug's free form. Through density functional theory studies, the molecular geometries of the three shortlisted medications (metformin, phenformin, and sitagliptin) and their HA conjugates were also investigated. The results demonstrate the pharmaceuticals' favorable molecular geometry towards pocket 3 of the aldose reductase target.

Giulio Rastelli et al. used a structure-based method to create novel aldose reductase (ALR2) inhibitors. The NCI chemical library was virtually screened using the DOCK tool to find compounds that complement the ALR2 active site. Five new compounds were found through this search that showed selectivity over ALR1 and inhibited ALR2 in the micromolar range. Interestingly, these substances do not fall into the well-researched and refined groups of aldose reductase inhibitors (ARIs), including carboxylic acids or spirohydantoins. Among these, a class of nitro-derivatives that showed great promise was found; they differed significantly in structure from the inhibitors that were already on the market. A round of structure-based design and synthesis improved this discovery even more. After optimization efforts, a derivative with a 10-fold increase in selectivity for ALR2 over ALR1 and a 10-fold improvement in IC50 was produced from a bioactive molecule with an IC50 of 42 μM. The sequence of nitro-derivatives' structure–activity relationships aligned with the way they bound to the ALR2 active site.

A thorough method for locating and creating possible therapeutic compounds that target aldose reductase, a crucial enzyme implicated in difficulties connected to diabetic mellitus (DM), is presented by Muhammad Yasir et al. To find a promising aldose reductase inhibitor, they used sophisticated computational methods with experimental validation by merging ligand-based and structure-based virtual screening methodologies. The approach showed a creative and effective approach to drug discovery and development in addition to making it easier to find a molecule with strong inhibitory potential. The discovered chemical, Z-565, may have therapeutic promise for the management of issues linked to diabetes mellitus if structural changes are made to improve its effectiveness.

One interesting class of naturally occurring substances with potential for use in medicine is the spirooxindole ring system. The potential of three dispirooxindolopyrrolizidines (DSOIP-H, DSOIP-Me, and DSOIP-OMe) as aldose reductase (AR) inhibitors was effectively shown in the work by Jibin K. et al. Their binding energy order was determined by molecular docking research, and the maximum affinity (-8.72 kcal/mol) was shown by DSOIP-OMe. Through hydrophobic interactions, all of the drugs demonstrated a significant binding to the catalytic active site of AR. Their promise as drug candidates was strengthened by the ADME analysis, which highlighted their advantageous pharmacokinetic characteristics. DSOIP-OMe was identified as the prospective inhibitor by molecular dynamics (MD) trajectory analysis and protein-ligand interaction studies because of its reliable interactions with important amino acid residues in the active site of AR. The results open the door for dispirooxindolopyrrolizidines to be further developed as therapeutic agents for the treatment of AR-related problems.

A new aldose reductase (AR) inhibitor called ranirestat (AS-3201) may be useful in treating diabetic sensory polyneuropathy. This study examined its effects on motor nerve conduction velocity (MNCV), its inhibitory mechanism on AR, and its influence on sorbitol levels in the sciatic nerves and lenses of rats with streptozotocin (STZ) diabetes. Ranirestat suppresses AR by a reversible and noncompetitive mechanism, according to kinetic

studies. In the sciatic nerves and lenses of STZ-diabetic rats, sorbitol levels were slightly decreased by a single oral dosage of ranirestat. This impact was further increased by repeated dosing over 5, 21, or 60 days; the maximum sorbitol reduction was seen after 21 days. The STZ-induced reduction in MNCV was improved dose-dependently by repeated oral ranirestat treatment for 21 or 42 days. These results show that repeated administration of ranirestat increases motor nerve conduction velocity and decreases sorbitol buildup in STZ-diabetic rats. This demonstrates its promise as a treatment for diabetic sensorimotor polyneuropathy.

CONCLUSION :

Aldose reductase (AR) plays a crucial role in diabetes complications, and the extensive collection of studies emphasizes the possibility of novel inhibitors as treatment approaches. By combining molecular docking, computational modeling, and experimental validation, interesting candidates with improved pharmacokinetic and binding affinity have been identified, opening up new treatment options for problems related to diabetes. In the polyol pathway, AR acts as the rate-limiting enzyme, turning glucose into sorbitol when blood sugar levels are too high. Complications like neuropathy, retinal, nephropathy, and cardiovascular problems are brought on by this process, which also causes oxidative stress, osmotic imbalances, and tissue damage. These results highlight AR as a key target for treatment. Dispirooxindolopyrrolizidines (DSOIP-H, DSOIP-Me, and DSOIP-OMe) have been shown by Jibin K. et al. to have potent AR inhibition. DSOIP-OMe had the strongest binding affinity and most reliable interaction with the active site of AR among them. HA-conjugated anti-diabetic drugs (metformin, phenformin, and sitagliptin) were investigated by D. Jayabal et al.; they found improved binding affinities and optimal geometries for AR suppression. In contrast to conventional inhibitor classes, Giulio Rastelli et al. discovered a novel family of nitro-derivatives with enhanced IC50 and selectivity for AR. Z-565 was discovered by Muhammad Yasir et al. to be a strong AR inhibitor with great promise for treating diabetes complications by combining ligand-based and structure-based virtual screening. In rats with STZ diabetes, ranirestat, an uncompetitive and reversible AR inhibitor, successfully decreased the buildup of sorbitol in the sciatic nerves and lenses. Motor nerve conduction velocity (MNCV) increased with repeated dosing, suggesting that it may be used to treat diabetic sensorimotor polyneuropathy.The combined study demonstrates the progress made in comprehending the pathophysiology of diabetes and the creation of tailored inhibitors for AR. Ranirestat and DSOIP-OMe are two emerging drugs that show great therapeutic promise. To address the worldwide burden of diabetes and its complications, more research and development of AR inhibitors using computational and experimental methods is necessary.

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