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RESEARCH ARTICLE

MOLECULAR MODELING OF ANGIOTENSIN TYPE 1 RECEPTOR FOR ANGIOTENSIN RECEPTOR BLOCKERS

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ABSTRACT

Diabetic nephropathy is characterized by progressive persistent proteinuria, hypertension, decline in renal function by decreasing glomerular filtration rate, and risk of cardiovascular disease. Recently, agents (ARBs) developed with antihypertensive and antiproteinuric efficacy that block the RAS by preventing angiotensin II from binding to its subtype1 (AT1) receptor, belong to the family of GPCRs. Hence efforts are to design the drug molecules to inhibition of angiotensin receptor blockers by using bioinformatics tools. SBDD confirms the angiotensin II binds to the AT1 receptor within the transmembrane domains in an extended conformation, and its C-terminal residue interacts with transmembrane domain VII at Phe-293/Asn-294.Methionine proximity assay, determine the molecular environment of this binding pocket (L112M and Y113M in TMD III; F249M, W253M, H256M, and T260M in TMD VI; and F293M, N294M, N295M, C296M, and L297M in TMD VII.). Based on information of Target protein id P30556 in Uniprot, Pubmed all and I-TASSER that allow to automatically generate high-quality predictions of 3D structure and biological function of protein molecules based on C-Score and TM-Score. SPICKER clustered simulated decoys and top five cluster centroids are selected for generating full atomic models. Target protein's ligand binding site was predicted by using both Q-Site Finder and Pocket Finder. Drug bank, clinical trials database was used for finding the drug molecule to blocking the angiotesin receptor type1 and drawing a ligand molecule in ACD/CHEMSKETCHI based on the ligand binding site and 2D-CORINA used in 2D to 3D convertions. Blind docking method dock the protein and small molecule at correct functional site. Based on Dock database calculation save the molecule in pdb format and view in PyMol and tools are used to finding the drug likeliness satisfying 5 Lipinski's rules.

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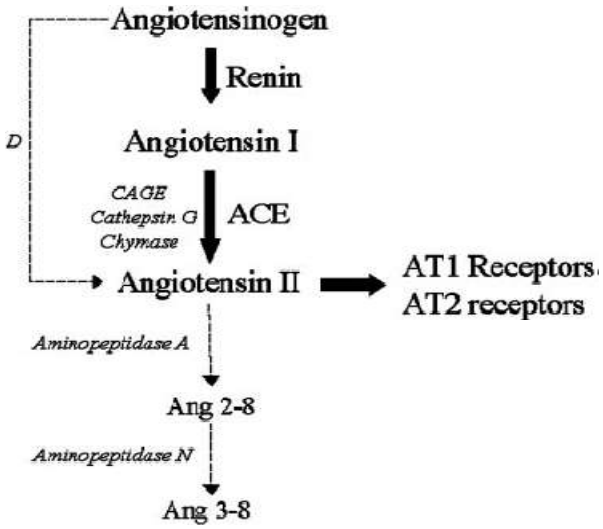
INTRODUCTION

Diabetic nephropathy is characterized by progressive proteinuria, hypertension, decline in renal function, and risk of cardiovascular disease. The pathogenesis and progression of diabetic nephropathy is multifactorial. The RAS plays an important role. Persistent proteinuria is the hallmark of diabetic nephropathy and suggests declining glomerular filtration rate. Reduction in proteinuria is associated with a slowing of the progression to end-stage renal disease and has been used as a surrogate endpoint for renal protection. Blood pressure reduction is the most significant factor in delaying onset and progression of renal disease. Blockade of the renin-angiotensin system (RAS) using angiotensin converting enzyme inhibitors (ACEIs) delays renal disease progression. More recently, agents that block the RAS by preventing angiotensin II from binding to its subtype 1 receptor (ARBs) have been developed in an effort to prevent deleterious consequences of pathologic levels of angiotensin II and to reduce the adverse effects of RAS blockade associated with ACEIs. Human studies with a variety of ARBs have clearly demonstrated the antihypertensive and antiproteinuric efficacy of these agents in patients with progressive renal diseases. Moreover, the effects of ARBs are similar or identical to those of ACEIs. Ongoing long-term clinical trials are designed to determine whether ARBs also preserve renal function similar to ACEIs.

Pathway of renin angiotensin system: The primary function of Ang II is the modulation of Na^+ reabsorption and H_2O retention in kidney in response to changes in extra cellular fluid volume. Thus, Ang II plays a major role in the regulation of blood pressure. Ang II also produces vasoconstriction. The responsiveness of blood vessels to Ang II varies between



tissues; while blood vessels in the kidney, mesentery and skin are highly responsive, blood vessels in the brain, lung and skeletal muscle are less responsive. Ang II also acts on the adrenal gland to increase the synthesis and release of aldosterone, which promotes reabsorption of Na^+ in the renal distal tubule. The angiotensin II has two subtype of receptors such as angiotensin type 1 receptor (AT1) and angiotensin type 2 Receptor (AT2), belong to the family of G-protein-coupled receptors (GPCRs). Hence efforts are to design the drug molecules to inhibition of angiotensin receptor blockers by using bioinformatics tools.

Structure based drug design (SBDD): The rational drug design in the field of GPCRs is vastly hampered by the unavailability of sufficient experimental structural information. Thus computational modeling was utilized to predict the 3D structure of the Angiotensin II Type 1 (AT1) receptor. The developed structural model was then extensively validated utilizing several structure-based and ligand-based techniques to prove the applicability of this model in prospective drug design and discovery. The peptide hormone angiotensin II (AngII) binds to the AT1 receptor within the transmembrane domains in an extended conformation, and its C-terminal residue interacts with transmembrane domain VII at Phe-293/Asn-294. The molecular environment of this binding pocket remains to be elucidated.

The preferential binding of benzophenone photo labels to methionine residues in the target structure has enabled us to design an experimental approach called the methionine proximity assay, which is based on systematic mutagenesis and photolabeling to determine the molecular environment of this binding pocket. A series of 44 transmembrane domain III, VI, and VII X --> Met mutants photolabeled either with 125I-(Sar1,p'-benzoyl-L-Phe8)AngII or with 125I-(Sar1,p''-methoxy-p'-benzoyl-L-Phe8)AngII were purified and digested with cyanogen bromide. Several mutants produced digestion patterns different from that observed with wild type human AT1, indicating that they had a new receptor contact with position 8 of AngII. The following residues form this binding pocket: L112M and Y113M in transmembrane domain (TMD) III; F249M, W253M, H256M, and T260M in TMD VI; and F293M, N294M, N295M, C296M, and L297M in TMD VII. Homology modeling and incorporation of these contacts allowed us to develop an evidence-based molecular model of interactions with human AT1 that is very similar to the rhodopsin-retinal interaction.

MATERIALS AND METHODS

Pubmed Central: The information about the target protein was collected from pub med central.

KEGG Database: KEGG is a database of biological systems, consisting of genetic building blocks of genes and proteins (KEGG GENES), chemical building blocks of both endogenous and exogenous substances (KEGG LIGAND), molecular wiring diagrams of interaction and reaction networks (KEGG PATHWAY), and hierarchies and relationships of various biological objects (KEGG BRITE). KEGG provides a reference knowledge base for linking genomes to biological systems and also to environments by the processes of PATHWAY mapping and BRITE mapping.

KEGG Maintains five main databases

KEGG Atlas: New interface to navigate pathway maps.
KEGG Pathway: Pathway maps and pathway modules.
KEGG Brite: Functional hierarchies and ontologies.
KEGG Genes: Genomes, genes, and proteins.

KEGG Ligand: Chemical compounds, drugs, glycans, and reactions. KEGG pathway database: Molecular interaction and reaction networks for metabolism, various cellular processes, and human diseases, It will be get it from manually entered from published materials. The information of target protein and renin angiotensin system pathway taken from this database. The KEGG, the Kyoto Encyclopedia of Genes and Genomes, was initiated by the Japanese human genome programme in 1995 pathway of Renin Angiotensin system

Uniprot

- The Universal Protein Resource (UniProt) is a comprehensive resource for protein sequence and annotation data. In 2002 the three institutes decided to pool their resources and expertise and formed the UniProt Consortium. The UniProt consortium was produces the important protein sequence databases are the UniProt Knowledgebase (UniProtKB), the UniProt Reference Clusters (UniRef), and the UniProt Archive (UniParc).
- UniProt is collaboration between the European Bioinformatics Institute (EBI), the Swiss Institute of Bioinformatics (SIB) and the Protein Information Resource (PIR). Across the three institutes close to 150 people are involved through different tasks such as database curation, software development and support. The protein sequences are derived from the translation of the coding sequences (CDS) which have been submitted to the public nucleic acid database, the EMBL-Bank/GenBank/DDBJ database. All these sequences, as well as the related data submitted by the authors, are automatically integrated into UniProtKB/TrEMBL.The UniProt/SWISS-Prot are generates the functional and non-redundant sequence databases. The information of the target protein was collected from this databases, the id is P30556.

Tasser

- I-TASSER server is an internet service for protein structure and function predictions. It allows academic

users to automatically generate high-quality predictions of 3D structure and biological function of protein molecules.

Tasser Generate the structure and Functions

- When users submit an amino acid sequence, the server first tries to retrieve template proteins of similar folds (or super-secondary structures) from the PDB library by LOMETS, a locally installed meta-threading approach.
- In the second step, the continuous fragments excised from the PDB templates are reassembled into full-length models by replica-exchange Monte Carlo simulations with the threading unaligned regions (mainly loops) built by ab initio modeling. In cases where no appropriate template is identified by LOMETS, I-TASSER will build the whole structures by ab initio modeling. The low free-energy states are identified by SPICKER through clustering the simulation decoys.
- In the third step, the fragment assembly simulation is performed again starting from the SPICKER cluster centroids, where the spatial restrains collected from both the LOMETS templates and the PDB structures by TM-align are used to guide the simulations. The purpose of the second iteration is to remove the steric clash as well as to refine the global topology of the cluster centroids. The decoys generated in the second simulations are then clustered and the lowest energy structures are selected. The final full-atomic models are obtained by REMO which builds the atomic details from the selected I-TASSER decoys through the optimization of the hydrogen-bonding network.
- The final results of function predictions are deduced from the consensus of top structural matches with the function scores calculated based on the confidence score of the I-TASSER structural models, the structural similarity between model and templates as evaluated by TM-score, and the sequence identity in the structurally aligned regions.
- The server is in active development with the goal to provide accurate structural and function predictions using state-of-the-art algorithms.
- The homepage and sequence submission page look like this i.e. followed by
- I was taken target protein model from this server based on the C-Score and TM- score I –TASSER.

C-score: C-score is a confidence score for estimating the quality of predicted models by I-TASSER. It is calculated based on the significance of threading template alignments and the convergence parameters of the structure assembly simulations. C-score is typically in the range of (-5,2), where a C-score of higher value signifies a model with a high confidence and vice-versa.

TM-Score: TM-score is a recently proposed scale for measuring the structural similarity between two structures (See Zhang and Skolnick, Scoring function for automated assessment of protein structure template quality, Proteins, 2004 57: 702-710). The purpose of proposing TM-score is to solve the problem of RMSD which is sensitive to the local error. Because RMSD is an average distance of all residue pairs in two structures, local errors (e.g. a misorientation of the tail) will araise a big RMSD value although the global topology is correct. In TM-score, however, the small distance is weighted stronger than the big distance which makes the score insensitive to the local modeling error. A TM-score >0.5 indicates a model of correct topology and a TM-score<0.17 means a random similarity. This cutoff does not depend on the protein length.

Cluster density: I-TASSER generates full length model of proteins by excising continuous fragments from threading alignments and then reassembling them using replica-exchanged Monte Carlo simulations. Low temperature replicas (decoys) generated during the simulation are clustered by SPICKER and top five cluster centroids are selected for generating full atomic models

For e.g.

Name	C-score	Exp.TM-Score	Exp. RMSD	No. of decoys	Cluster Density
Model1:	0.28	0.75+-0.10	6.0+-3.7	3830	0.3030
Model2:	-1.45			681	0.0536
Model3:	-1.81			430	0.0374
Model4:	-2.19			363	0.0256
Model5:	-2.86			159	0.0130

Drug bank: The Drug Bank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.

Pocket-finder and q-site finder: The tool was used for prediction of functional sites or active sites.

Q-Site Finder: Q-SiteFinder is a new method of ligand binding site prediction. It works by binding hydrophobic (CH3) probes to the protein, and finding clusters of probes with the most favourable binding energy.

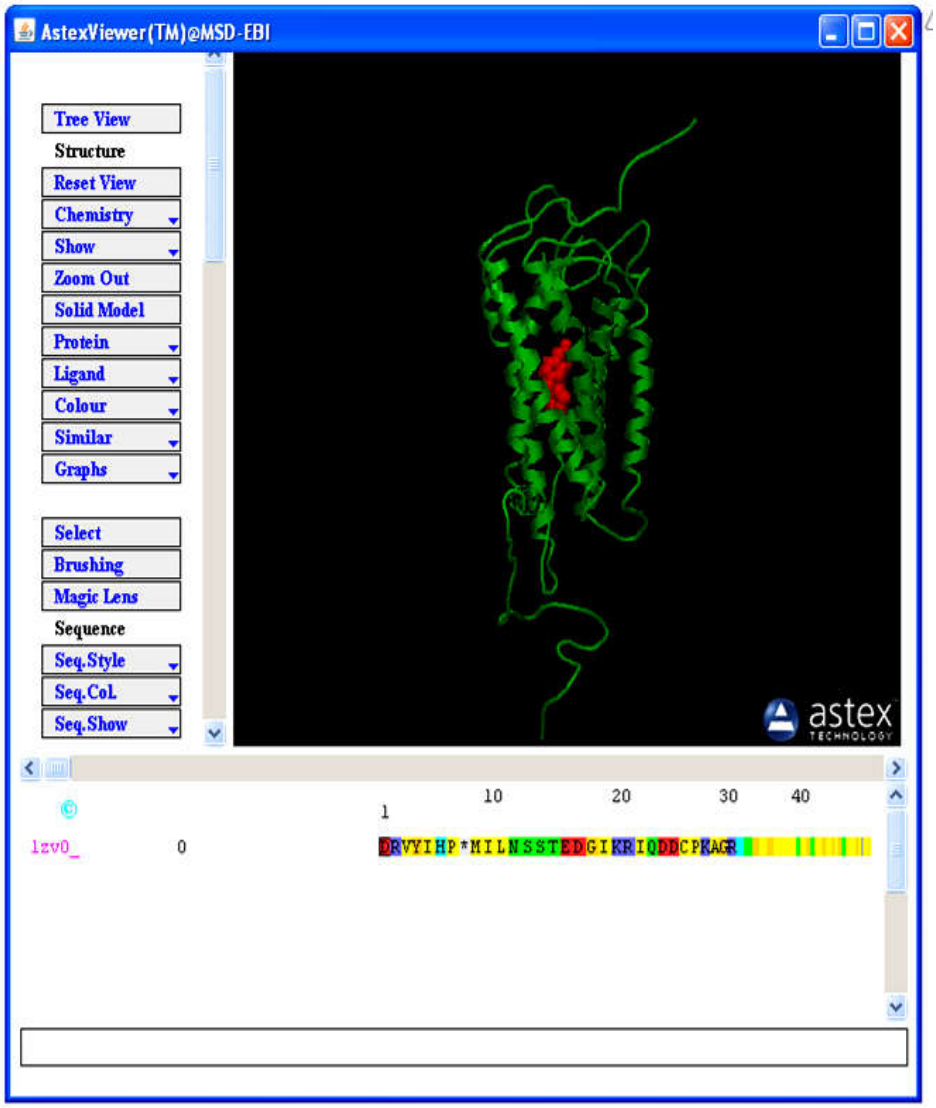
Pocket-Finder: Pocket-Finder is a pocket detection algorithm based on Ligsite written by Hendlich *et al* (1997). Pocket-Finder works by scanning a probe radius 1.6 angstoms along all gridlines of a grid resolution 0.9 angstroms surrounding the protein. Both Q-SiteFinder and Pocket-Finder allow you to upload a PDB file or select one from the Protein Database. The target protein ligand binding site was predicted by using both Q-Site Finder and Pocket Finder.

Clinical trials: The clinical trials database was used for finding the drug molecule to blocking the angiotesin receptor type 1.

ACD/Chemsketch: Academic institutions worldwide have adopted this software as an interactive teaching tool to simplify and convey chemistry concepts to their students, and publishing bodies such as Thieme**,** the publisher of Science of Synthesis, consider it to be "supportive of the organic chemistry publisher's role, both in the construction of compounds and their basic analysis." ACD/ChemSketch is also available as freeware, with functionalities that are highly competitive with other popular commercial software packages. The freeware contains tools for 2D structure cleaning, 3D optimization and viewing, InChI generation and conversion, drawing of polymers, organometallics, and Markush

structures—capabilities that are not even included in some of the commercial packages from other software producers. Also included is an IUPAC systematic naming capability for molecules with fewer than 50 atoms and 3 rings. The capabilities of ACD/Chem Sketch can be further extended and customized by programming. So it has many features using this tool I was draw aligand molecule based on the ligand binding site. The 3d optimization of the drug also done by using this software. The followed analogue was drawn by based on the losartan.

The following tools are used to finding the drug likeliness



2D-Corina

Corina: Fast and Efficient Generation of High-Quality Three-Dimensional Molecular Models. The input format for this server please enters the SMILES format to the modeled ligand. It was used 2D to 3Dconvertions.

Argus Lab: Dr. Thompson is an expert in theoretical and computational chemistry. He has published and spoken widely in the areas of photosynthesis, molecular recognition, and the development of hybrid QM/MM methods. He has 20 years experience developing and implementing novel algorithms to solve challenging scientific and industrial problems in computational chemistry, drug modeling, scientific visualization, and enterprise business software systems. At Planaria, he authored the Argus Lab molecular modeling program currently used by more than 20,000 scientists and students worldwide.

Docking: This is computational chemistry software, so it will be very useful for energy minimization. Then we could able to build small molecule using this window tools. And also do the lead optimizations. The target protein and small molecule was docked by Argus lab, it was done by blind docking method.

Blind docking means we couldn't want to specify the active site, ligand was correctly to bind the functional site. After the dock database calculation we want to save the molecule in pdb format and then view PyMol (Molecule Visualization tool).

Pymol

PyMOL is good for

- Viewing 3D molecular structures
- Rendering Figures Artistically
- Animating Molecules Dynamically
- Giving Live 3D Presentation
- Sharing Interactive Visualization

Lipinski's rule of five: Checks whether a drug satisfies the 5 Lipinski's rules. Lipinski rule of 5 helps in distinguishing between drug like and non drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules. The Lipinski Filter was used for this tool analyzing the ligand.

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

In IIT to develop this software for novel scientific methods and highly efficient algorithms for Genome analysis, Protein structure prediction and active site directed Drug Design.

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