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INSILICO DOCKING STUDIES OF 11-BETA HYDROXYSTEROID DEHYDROGENASE AS A POTENTIAL DRUG TARGET FOR ASTHMA

ARUL JAYAN[1], MOHANRAJ[2], ANBARASU[3] AND JERRINE JOSEPH*[4]

[1,2]Department of Chemical Engineering, Sathyabama University, Chennai-600119.
[3,4]Centre for Drug Discovery and Development, Sathyabama University, Chennai-600119.

ABSTRACT

Asthma is a chronic respiratory syndrome. An Insilco study to identify possible drug target for blocking the 11-beta hydroxysteroid dehydrogenase (11-βHSD) enzyme that catalyses the conversion of hydrocortisone to cortisone in the cholesterol metabolism the level of hydrocortisone, which plays a vital role in the control of asthma has been attempted. The inhibition of 11-βHSD by glycyrrhetinic acid, resulted in halting the inflammation in the epithelial cells and ultimately controlling the allergy and Asthma. In this work, we carried out docking studies of the protein 11-βHSD and ligand. Glycyrrhetinic acid, which reveals a better binding of the ligand to the protein. ME Dock, Patch Dock, Hex dock, Gold Dock has been used in this study to reveal the binding. The docking programs successfully works by binding the protein and the ligand gives very useful data about the enzyme values, hydrogen bonds between them, hydrophobic bonds, inter atomic contents between them, and the neighboring amino acids to which the drug has contact. All these studies will give insight in determining the property of the drug.

Keywords: **Asthma, 11-βHSD, Glycyrrhetinic acid, docking studies**

*Corresponding author

JERRINE JOSEPH
Centre for Drug Discovery and Development,
Sathyabama University, Chennai-600119

INTRODUCTION

Asthma is a disease that is caused due to the inflammation of the pulmonary airways and bronchial hyper responsiveness. Bronchial asthma is one of the crippling conditions approximately 8% of the global populations are affected with this malady[1]. A variety of exogenous stimulants of asthma are present some of which are air pollution, tobacco smoking, diet, occupation and respiratory infection, these pollutants act as causative agents may elicit asthmatic reaction in airways that are already susceptible and hyper responsive[2]. In allergic respiratory diseases, several native medication through traditional knowledge have been used as conservative therapy in asthma. Among all the existing therapeutic measures available polyherbal amalgamations are said to be well-accepted, anodyne and operative in asthma[3,4]. The reason for the beneficial ability of herbal combinations in asthma is due to several obstructive and homeostasis of very multifaceted and reliant cellular and intermediary lattices auxiliary and involved in the stimulating process of asthma[5]. Asthma has been treated with many drugs and with different routes of administration. Generally steroids are used to control Asthma. 11β - Hydroxy steroid Dehydrogenase (11βHSD) reversibly converts hydrocortisone, the predominant active endogenous glucocorticoid in humans, to its inactive metabolite cortisone by oxidizing the 11-Hydroxy group to an 11- Keto group. Since this enzyme is highly expressed in human bronchial epithelial cells, it is hypothesized that it regulates epithelial responses to glucocorticoids by reducing levels of hydrocortisone available to bind to the glucocorticoid receptor. Glycyrrhetinic acid, is similar in structure to glucocorticoids and has antagonist activity. Glycyrrhetinic acid, a compound derived from licorice extracts and is known for anti-inflammatory properties [6-9]. Inhaled and systemic glucocorticoids are highly effective anti-inflammatory agents that are the mainstay of therapy for numerous inflammatory conditions such as atopic dermatitis, inflammatory bowel disease, collagen vascular disease and Asthma. Thus glycyrrhetinic acid is the drug that is used to inhibit the activity of 11βHSD and it stops the conversion of hydrocortisone to cortisone[10].

11βHSD1 (variously termed as HSD11L) is a ~35 kDa glycosylated membrane-protein, oriented into the lumen of endoplasmic reticulum. This isoform is the sole 11β-reductase in the body and exerts two separate enzymatic activities: 11β-dehydrogenase (cortisol to cortisone) and 11-oxoreductase (cortisone to cortisol) in vitro; however, in vivo, it acts mainly as reductase producing active cortisol. The enzyme also plays an important role in xenobiotic carbonyl compound detoxification processes. 11β-HSD1 is expressed in a wide array of tissues, with highest levels in Liver and adipose tissues. Glycyrrhetinic acid has also been suggested to be helpful in other disease typically treated by glucocorticoids including eczema and addisons disease. Despite its structural similarly to glucocorticoids (GA) binds poorly to the glucocorticoid receptor. Glycyrrhetinic acid – a saponin isolated from licorice root (Glycyrrhizae radix). It has a similar structure of glucocorticoids. It has been known that glycyrrhetinic acid can inhibit 11 β -HSD activity[11,12]. Docking programs are used to study the properties of binding of the enzyme and ligand. An x-ray crystallographic or NMR structure may be used for the design of ligands and it must be examined to determine where the ligands are likely to bind. In the absence of an experimental structure of the protein of interest complexed with ligand, it is not a trivial exercise to locate these sites. Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion or van der Waals, hydrogen bonding and electrostatic (ion pairing). The major driving force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Determining the optimum fit and interaction energy of a ligand in a known receptor site remains difficult. Most

high affinity receptors are located on a concave surface of the protein. However, these may be several concave surfaces and it is difficult to determine which of there is responsible for binding. Once the binding site has been identified, it is often necessary to refine (or) augment the experimental structure. Docking of ligands to proteins is a difficult problem since it involves optimization of six degrees of freedom between the ligand and the protein as well as optimization of internal torsional degrees of freedom in the ligand. Hence, the research work presents the key events and players in 11 β hydroxysteroid dehydrogenase inhibition and discusses a new drug target in the prevention of inflammatory disease with the help of the Maximum Entropy Dock, Hex Dock, patch dock and Gold dock programmes.

MATERIALS AND TOOLS

Docking Programs

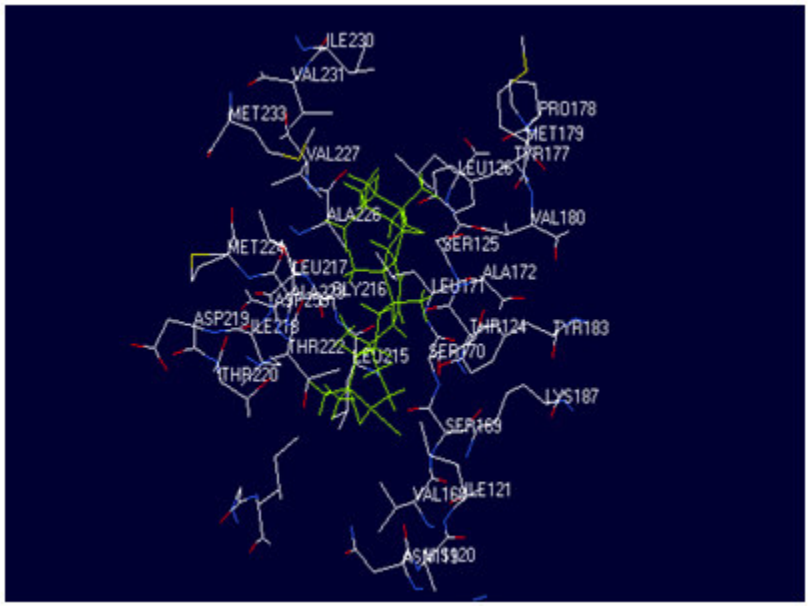
ME Dock

The design of the ME Dock (Maximum Entropy based Docking) web server, which is aimed at providing an efficient utility for the prediction of ligand binding sites. Therefore, the search should be governed by a bell-shaped probability distribution. The main reason why the Gaussian distribution is employed in the design of ME Dock is because the Gaussian distribution has the maximum entropy, provided that the variance of the distribution is fixed. Since, in information theory, entropy means randomness. ME means maximum randomness. ME Dock converged to the correct binding modes while consuming significantly smaller numbers of energy evaluations. Given a threshold for the number of energy evaluations used in the docking simulation, ME Dock also greatly elevated the rate of accurate prediction for all benchmark cases.

RESULTS

Figure 1

Shows the docked image of the ligand with the enzyme.



Hex Dock

Hex uses a simple clustering algorithm to group spatially similar docking orientations. Each docking solution is first ordered by energy, and the lowest energy solution is made the seed orientation for the first cluster. The list is then searched for other similar orientations whose main-chain alpha-Carbon RMS deviation is within a given threshold (default 2Å RMS) of the seed orientation, and these orientations are then assigned to the first cluster.

Patch Dock

This method performs structure prediction of protein–protein and protein–small molecule complexes. The algorithm was verified on enzyme–inhibitor and antibody–antigen complexes from benchmark 0.0, where it successfully found near-native solutions for most of the cases. The algorithm was also successfully tested in the last three rounds of the Critical Assessment of Prediction of Interactions (CAPRI)[13-16] .The above figure shows that the neighboring amino acid residues, which is closed to the ligand docked to the enzyme. Docking of the enzyme with the inhibitor in patch dock showed the maximum score of 6152 with an area of 670.62.

DISCUSSION

The docking programs ME Dock, Hex Dock, Patch Dock, Gold dock enabled the ligand to bind to the protein (11-betaHSD) successfully and revealed the properties of the complex. The docking programs suggest that the Glycyrrhetinic acid is a good natural inhibitor of 11BHSD. The docking programs revealed lots of details about the complex (ie.,) Hydrogen bonding, Inter atomic contacts, The neighboring amino acids to which the drug has contact and the energy values and scores helps us to understand their docking efficiency.

CONCLUSION

Based on the docking studies and analysis of the results obtained from different docking programs, it is concluded that these findings will unravel the mystery of deciphering the ligand protein interactions. The insight provided will enable us further evaluate and validate the hypothesis in wetlab to get new lead molecules in the control of Asthma.

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