Drug Discovery

RESEARCH

ISSN 2278 – 540X EISSN 2278 – 5396

Study of Junctopholin 2 (JPH2) protein and its binding efficiency with herbal and allopathic antibiotics

Publication History
Received: 08 March 2015
Accepted: 23 March 2015
Published: 1 April 2015

Citation
Sathish P, Ruba Glory P, Palanivelu K. Study of Junctopholin 2 (JPH2) protein and its binding efficiency with herbal and allopathic antibiotics. *Drug Discovery*, 2015, 10(24), 45-55

STUDY OF JUNCTOPHOLIN 2 (JPH2) PROTEIN AND ITS BINDING EFFICIENCY WITH HERBAL AND ALLOPATHIC ANTIBIOTICS

P. Sathish, P. Ruba Glory and K. Palanivelu*

P.G and Research Department of Zoology, Govt.Arts College (Autonomous), Kumbakonam – 612 001, Tamil Nadu, India.

ABSTRACT

This study is aimed to determine the effect of drug (herbal and allopathic) on the JPH2. JPH2 protein sequence was collected from Uni-Prot. The composition of amino acids was determined by using Protparam. The tertiary structure of JPH2 was predicted by using CPH modeling server and visualized through Rasmol. Ramachandran plot was performed for JPH2 using Rampage software. The active sites were predicted by CASTp. The docking of Junctophilin-2 protein with selected one herbal antibiotic (TOCOPHEROL) and one allopathic antibiotic (BISOPROLOL) was performed by the use of the tool Hex 6.3

Keywords: JPH2, Heart failure, Herbal drug, Allopathic drug, Predicted.

Corresponding Author: palanivelu59@gmail.com, slotraufrubaglory@gmail.com

INTRODUCTION

Bioinformatics is an interdisciplinary research area at the interface between computer science and biological science. Bioinformatics involves the technology that uses computers for storage, retrieval, manipulation and distribution of information related to biological macromolecules such as DNA, RNA and proteins.

HEART FAILURE

Heart failure (HF), often used to mean chronic heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the needs of the body [Donagh and Theresa, 2011]. The terms congestive heart failure (CHF) or congestive cardiac failure (CCF) are often used interchangeably with chronic heart failure [Eyal Herzog, 2012].

Common causes of heart failure include coronary artery disease including a previous myocardial infarction (heart attack), high blood pressure, atrial fibrillation, valvular heart disease and cardiomyopathy [Dickstein *et al*., 2008].The severity of disease is usually graded by how much the ability to exercise is decreased [Taylor *et.al*., 2014]. Treatment depends on the severity and cause of the disease [Jessup *et.al*., 2009]. In people with chronic disease already in a stable situation, treatment commonly consists of lifestyle measures such as stopping smoking, physical exercise and dietary changes, as well as medications [Baldasseroni *et.al*., 2002].

Termiology:

Heart failure is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs. The term "congestive heart failure" (CHF) is often used as one of the common symptoms is swelling or water retention [Fonarow *et.al*., 2008]. Ejection fraction is

the proportion of blood in the heart pumped out of the heart during a single contraction [Nieminen *et al*., 2005]. It is a percentage with normal being between 50 and 75%.

Heart failure may also occur in situations of "high output," (termed "high output cardiac failure") where the ventricular systolic function is normal but the heart can not deal with an important augmentation of blood volume [Ogden *et.al*., 2001]. There are several other exceptions to a simple left-right division of heart failure symptoms. Left sided forward failure overlaps with right sided backward failure[Rang, 2003]. Congestive heart failure occur in overload situation, renal diseases, chronic severe anemia, beriberi, thyrotoxicosis, Paget's disease, arteriovenous fistulae or arteriovenous malformations [Boron *et.al*., 2005]. Ischaemic heart disease 62%, Cigarette smoking 16%, Hypertension (high blood pressure) 10%, Obesity 8%, Diabetes 3%, Valvular heart disease 2%.

Epidamology of Heart Failure: The United Kingdom and more than $35 billion in the United States. Heart failure is the leading cause of hospitalization in people older than 65. In developed countries, the mean age of patients with heart failure is 75 years old. Two to three percent of the population have heart failure, but in those 70 to 80 years old, it occurs in 20–30 percent.

JUNCTOPHILIN PROTEIN

Junctophilin 2, also known as JPH2, is a protein which in humans is encoded by the JPH2 gene [Takeshima and Komazaki *et.al*., 2000]. Junctional complexes between the plasma membrane and endoplasmic sarcoplasmic reticulum are a common feature of all excitable cell types and mediate cross talk between cell surface and intracellular ion channels [Nishi *et.al*., 2000]. JPH2 is a member of the junctophilin gene family (the other members of the family are

JPH1, JPH3 and JPH4) and is the predominant isoform in cardiac tissue, but is also expressed with JPH1 in skeletal muscle [Garbino *et.al.,* 2009]. The JPH2 protein product plays a critical role in maintaining the spacing a geometry of the cardiac dyad - the space between the plasma membrane and sarcoplasmic reticulum [Landstrom *et.al.,* 2007].

HERBAL DRUG

Tocopherol is a class of organic chemical compounds many of which have vitamin E activity. Because the vitamin activity was first identified in 1936 from a dietary fertility factor in rats, it was given the name "tocopherol" from the Greek word. α-Tocopherol is the main source found in supplements and in the European diet, where the main dietary sources are olive and sunflower oils, while γ-tocopherol is the most common form in the American diet due to a higher intake of soybean and corn oil

ALLOPATHIC DRUGS:

Bisoprolol is a drug belonging to the group of beta blockers, a class of medicines used primarily in cardiovascular diseases. More specifically, it is a selective type β1 adrenergic receptor blocker. The U.S. Food and Drug Administration (FDA) approved an application by Duramed Pharmaceutical for Zebeta Oral Tablets (Bisoprolol Fumarate) as a new molecular entity on July 31, 1992 [Buhring *et.al.,* 1986]. It is beneficial in treatment for: high blood pressure (hypertension), reduced blood flow to the heart (cardiac ischemia);congestive heart failure, preventative treatment before and primary treatment after heart attacks decreasing the chances of recurrence [Rosenberg *et.al.,* 2008]. During hypertension there is an elevated blood pressure, which is what bisoprolol targets [Amabile and Serradimigni, 1987].

MATERIALS AND METHODS

The structure of Junctophilin-2 (JPH2) protein were predicated with the help of bioinformatics tools and also docking with selected antibiotic such as herbal drug use of Drug bank (Tocopherol) and allopathic drug use of (Bisoprolol) were analyzed (Fig 1, 2). Human Junctophilin-2 protein sequence was retrieved from the UNI-PORT protein sequence data base. By the use of CFSSP the secondary structure was determined. The tertiary structure of JPH2was predicted by using CPH 3.2 server and visualized using Rasmol. The Ramachandran plot was performed for JPH2 by using Rampage software. CASTp predicted the active sites.

RESULTS

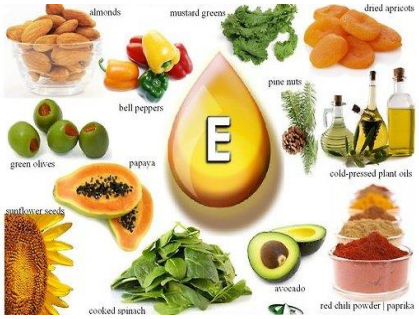
Human Junctophilin-2 (JPH2) sequence was retrieved from the UNI-PORT protein sequence data base. The structure of JPH2 protein was predicated with the help of Bioinformatics tools and also docking with selected antibiotic such as herbal drug (Tocopherol) and allopathic drug (Bisoprolol) was analyzed (Table 1).

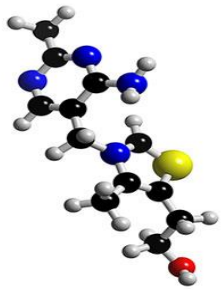
Amino acid composition was determined for the human Junctophilin-2 protein. Junctophilin-2 protein has 696 amino acids with the molecular weight of 74221.5. It's theoretical PI is 8.82. The aliphatic amino acids Alanine is present in highest number (84). Further the amino acids Glycine, Glutamic acid, Proline, Serine and Arginine are also higher in number as 82, 61, 60, 60 and 53 respectively.The negatively charged amino acid aspartic is lesser than the glutamic acid. The positively charged amino acid arginine is higher than the Lysine. It has the estimated half-life of 30hours. Its instability index is 60.75 and its aliphatic index is 60.45. It has the grand average of hydropathicity - 0.709. Junctophilin-2 protein has 10324 atoms. Among them the carbon, hydrogen, nitrogen, oxygen and sulphur atoms are present in 3237, 5089, 969,

1018 and 11 numbers respectively. The secondary structure of Junctophilin-2 protein has alpha helix, 47.8% extended strand, 16.4 % beta turns and 17.1% random coil.

The Ramachandran plot showed that Junctophilin-2 protein has 696 amino acids (89.8%) are in favoured region 18 (7.1%) are in allowed region and 8 (3.1%) is in outlier region. This proves that the predicated model is acceptable.CASTp predicated the active sites. Junctophilin-2 protein structure has 36 active sites. Junctophilin-2 protein has four large active sites (33,34,35 and 36) and one small active site (9). Docking of Junctophilin-2 protein with selected one herbal antibiotic (TOCOPHEROL) and one allopathic antibiotic (BISOPROLOL) were performed by the use of the tool Hex 6.3 Heart Failure antibiotics TOCOPHEROL and BISOPROLOL have showed higher binding efficiency, ie -264.73 and ie -232.45 respectively with Junctophilin-2 protein when compared with the herbal and allopathic antibiotics.

Fig :1 - Herbal drug: Tocopherol Chemical Structure





Allopathic drugs: Bisoprolol Chemical structure

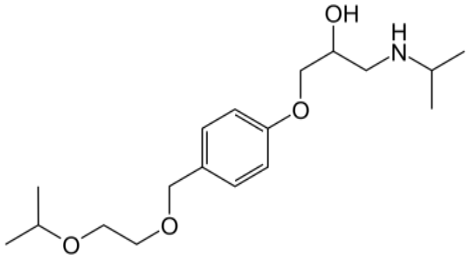
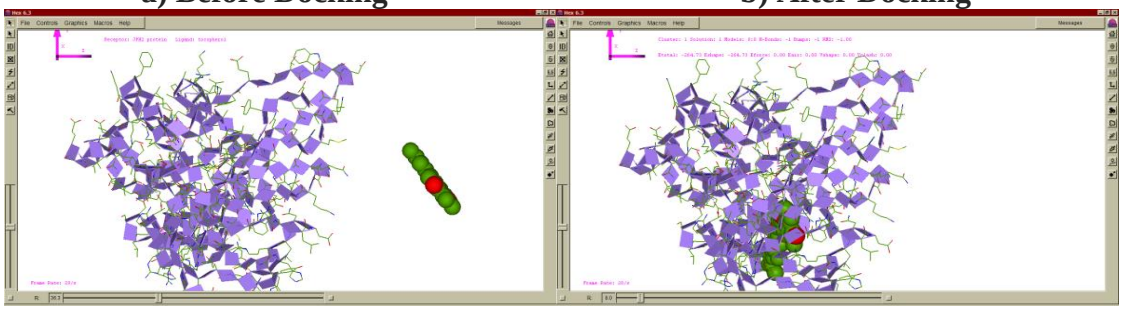


Fig: 2 - Herbal Drug Docking: Heart failure JPH2 protein with Tocopherol

a) Before Docking **b) After Docking**



Allopathic Drug Docking: Heart failure JPH2 protein with Bisoprolol

a) Before Docking **b) After Docking**

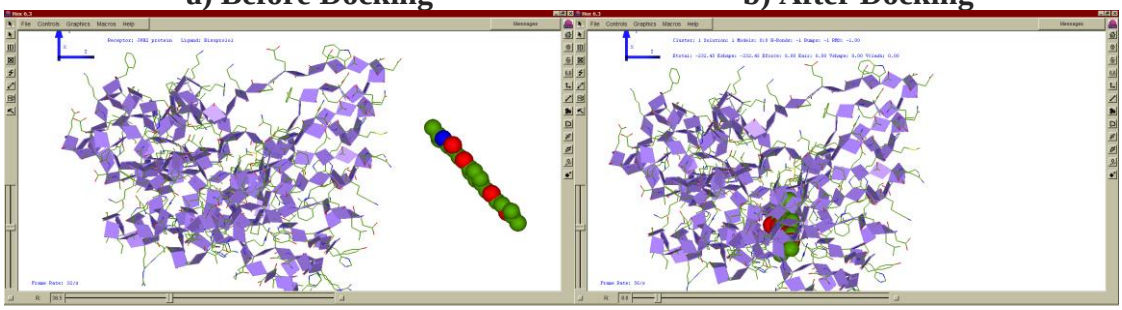


Table: 1- Herbal Drugs and Allopathic Drugs docking in: Heart failure JPH2

HERBAL DRUG					
LIGAND	E.TOTAL	E.SHAPE	E.FORCE	BUMPS	RMS
Tocopherol	**-264.73**	**-264.73**	**0.00**	**-1**	**-1.00**
ALLOPATHIC DRUG					
LIGAND	E.TOTAL	E.SHAPE	E.FORCE	BUMPS	RMS
Bisoprolol	**232.45**	**-232.45**	**-0.00**	**-1**	**-1.00**

DISCUSSION

Docking of Junctophilin-2 protein with selected herbal and allopathic antibiotics such as Tocopherol and Bisoprolol were performed by the use of the tool HEX 6.3. Tocopherol and Bisoprolol have showed higher binding effiiciences, ie -264.73 and ie -232.45 respectively with Junctophilin-2 protein when compared with the herbal and allopathic (Table 1).

REFFERENCE

1. **Amabile, G and Serradimigni, A. (1987).** "Comparison of bisoprolol with nifedipine for treatment of essential hypertension in the elderly: Comparative double-blind trial".European heart journal. 8 Suppl M: 65–69. PMID 2967187

2. **Baldasseroni S; Opasich C; Gorini M and Lucci D, (2002).** "Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure".American Heart Journal 143 (3): 398–405.doi:10.1067/mhj.2002.121264.PMID 11868043.

3. **Boron, Walter F.; Boulpaep and Emile L. (2005).** Medical Physiology: A Cellular and Molecular Approach (Updated ed.). Saunders. p. 533. ISBN 0-7216-3256-4.

4. **Bühring KU, Sailer H, Faro HP, Leopold G, Pabst J and Garbe A (1986).** "Pharmacokinetics and metabolism of bisoprolol-14C in three animal species and in humans". J. Cardiovasc. Pharmacol. 8 Suppl 11: S21–8. PMID 2439794.

5. **Dickstein K, Cohen-Solal A and Filippatos G (2008).** "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology.Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)". Eur. Heart J. 29 (19): 2388–442. doi:10.1093/eurheartj/ehn309.PMID 18799522.

6. **Donagh and Theresa A. (2011).** Oxford textbook of heart failure. Oxford: Oxford University Press. p. 3. ISBN 9780199577729.

7. Eyal Herzog (2012). The Cardiac Care Unit Survival Guide. Lippincott Williams & Wilkins. p. 98. ISBN 9781451177466.

8. Fonarow GC, Abraham WT and Albert NM (2008). "Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes:OPTIMIZE-HF".Arch. Intern. Med. 168 (8): 847–854. doi:10.1001/archinte.168.8.847.PMID 18443260.

9. Garbino A and van Oort RJ (2009). "Molecular evolution of the junctophilin gene Family. "Physiol Genomics 37 (3):175-86 dog :10. 1152/physiolegenomics 00017.2009 PMC 2685503. PMID 19318539.

10. Jessup M, Abraham WT and Casey DE (2009). "focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines"119(14):1977–2016.doi:10.1161/ CIRCULATIONAHA.109.192064. PMID 19324967.

11. Landstrom AP and Weisleder N (2007). "Mutations in JPH2-encoded junctophilin-2 associated with hypertrophic cardiomyopathy in humans". J Mol Cell Cardiol 42(6): 026–35.doi:10.1016/j.yjmcc.2007.04.006. PMID 17509612.

12. Nieminen MS, Bohm M and Cowie MR (2005). "Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology".Eur. Heart J. 26 (4): 384–416.doi:10.1093/eurheartj/ehi044. PMID 15681577.

13. **Nishi M, Mizushima A, Nakagawara K and Takeshima H (2000).** "Characterization of human junctophilin subtype genes".Biochem. Biophys. Res. Commun. 273 (3): 920–7. doi:10.1006/bbrc.2000.3011. PMID 10891348.

14. **Ogden LG He J; Bazzano LA and Vupputuri S (2001).** "Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study".Arch. Intern. Med.161 (7): 996–1002. doi:10.1001/archinte.161.7.996. PMID 11295963.

15. **Rang HP (2003).** Pharmacology. Edinburgh: Churchill Livingstone. p.127.ISBN 0443-07145. Rosenberg, J and Gustafsson, F. (2008). "Bisoprolol for congestive heart failure". Expert opinion on Pharmacotheraphy 9 (2): 293- 200. Doi: 10.1517/14656566.9.2.293. PMID 18201151.

16. **Takeshima H, Komazaki S, Nishi M, Iino M and Kangawa K (2000). "**Junctophilins: a novel family of junctional membrane complex proteins".Mol. Cell 6 (1): 11–22. doi:10.1016/S1097- 2765(05)00005-5. PMID 10949023.

17. **Taylor, RS; Sagar, VA; Davies, EJ; Briscoe, S; Coats, AJ; Dalal, H; Lough, F; Rees, K, Singh, S 27, (2014).** "Exercise-based rehabilitation for heart failure.".The Cochrane database of systematic reviews 4: CD 003331 doi 101002/14651858 CD003331 pub 4. PMID 24771460.