Molecular docking study of tripeptides VPP and IPP inhibiting angiotensin I converting enzyme to alleviate high altitude pulmonary edema

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High altitude pulmonary edema (HAPE) remains the major cause of death related to high altitude exposure with a high mortality in absence of emergency treatment. Due to the deprival of oxygen in higher altitudes, the blood vessels constricts and squeezes blood in the vessels. This makes pressure to go up which in turn forces blood into air pockets in lungs that can kill people with HAPE. Angiotensin Converting Enzyme (ACE) is found in lung capillaries. It catalyses conversion of angiotensin I to angiotensin II which is a potent vasoconstrictor and inactivates bradykinin which is a potent vasodilator thereby causing HAPE. Tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) act as ACE inhibitors that reduce vasoconstriction and facilitate vasodilation, so that they can be used in the treatment of HAPE. Enzyme-inhibitor docking is performed between Angiotensin I Converting Enzyme ACE and two natural inhibitors, tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) using the Patchdock Software. The docking study provided a quantitative energetic measure (Atomic Contact Energy) of 262.56 and 147.73 for ACE inhibition by VPP and IPP respectively. This ensures that the tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) are able to inhibit the activity of the ACE which in turn can induce decreased formation of Angiotensin II and decreased inactivation of bradykinin thereby it can alleviate HAPE.

Key words: High Altitude Pulmonary Edema (HAPE), angiotensin converting enzyme, Val-Pro-Pro, Ile-Pro-Pro, patchdock.

INTRODUCTION

High Altitude Pulmonary Edema (HAPE) is a life-threatening form of non-cardiogenic pulmonary edema that occurs in otherwise healthy mountaineers at altitudes above 2,500 m (Roach et al., 2002). In some people it might also occur at lower altitudes that is between 1500 and 2500 m. It remains the major cause of death related to high altitude exposure with a high mortality in absence of emergency treatment. It is caused by the shortage of oxygen which occurs due to the lower air pressure at high altitudes. Due to the deprival of oxygen the lung reacts in the same way that blood vessels constrict. The blood in these vessels gets squeezed and the pressure goes up forcing fluid out of blood and into air pockets that can kill people with HAPE (Kenneth et al., 2006). Even though the mechanisms by which the shortage of oxygen causes HAPE are poorly understood there are two processes that are believed to be important causative factors. One factor is increased pulmonary arterial and capillary pressures (pulmonary hypertension) secondary to hypoxic pulmonary vasoconstriction (Bärtsch et al., 1991). Another factor is an idiopathic non-inflammatory increase in the permeability of the vascular endothelium (Swenson et al., 2002). It is considered that genetic basis can be a cause to this condition. Also, there is an involvement of a gene for Angiotensin Converting Enzyme (ACE) causing this condition.

ACE

Angiotensin I Converting Enzyme (ACE) is an exopeptidase. It is found mainly in lung capillaries. It catalyses conversion of angiotensin I to angiotensin II which is a potent vasoconstrictor. It is involved in the inactivation of
bradykinin, a potent vasodilator. These two actions of ACE make it an ideal target in the treatment of conditions such as high blood pressure, heart failure and diabetic nephropathy type 2 diabetes mellitus. Since inhibition of ACE by usage of ACE inhibitors results in decreased formation of Angiotensin II and decreased inactivation of bradykinin, it can be used as an ideal target for HAPE.

ACE Inhibitors

ACE inhibitors are a group of pharmaceuticals that are used primarily in treatment of hypertension and congestive heart failure. ACE inhibitors reduce vasoconstriction and facilitate vasodilation, thereby it can lead to a way to treat HAPE. There are a number of chemicals like captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, and fosinopril function as ACE inhibitors. Also, naturally occurring ACE inhibitors include casokinins and lactokinins are breakdown products of casein and whey (FitzGerald et al., 2004).

Tripeptides VPP and IPP

Apart from the chemical and natural inhibitors of ACE, there are tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) produced by the probiotic Lactobacillus helveticus have been shown to have ACE-inhibiting and antihypertensive functions (Nakamura et al., 1995; Aihara et al., 2005). It is also shown that L. helveticus fermented milk had an antihypertensive effect after oral administration to spontaneously hypertensive rats (Nakamura et al., 1995).

VPP and IPP are associated with the antihypertensive effect of L. helveticus fermented milk (Masuda et al., 1996). Efficacy of L. helveticus fermented milk containing VPP and IPP has been tried in hypertensive patients by ingesting fermented milk drink on a daily basis for 8 weeks (Hata et al., 1996). It is thought to be more effective to consume the fermented milk as part of the diet during the early stages of a therapeutic plan for hypertension or for prevention of the incidence of hypertension. Studying the efficacy and safety of powdered L. helveticus fermented milk tablets on subjects with hypertension revealed that, foods containing powdered L. helveticus fermented milk could be used in dietary approaches to the primary prevention of hypertension (Aihara et al., 2005). Tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) can reduce vasoconstriction and facilitate vasodilation, thereby it can lead to a way to treat HAPE.

This work is of vital importance for the development of new therapeutics to decrease formation of Angiotensin II and to decrease inactivation of bradykinin as a means of inhibiting ACE, thereby it can alleviate HAPE.

METHODOLOGY

PDB

PDB is one of the repositories for 3-D structural data of proteins and nucleic acids. The PDB database is operated by the research collaboratory for structural bioinformatics (RCSB). As at March 3, 2009 PDB had 56217 macromolecular structure data entries.

Retrieval of angiotensin I converting enzyme (ACE)

Crystal structure of angiotensin I converting enzyme (ACE) from the organism Homo sapiens with the PDB ID 1O8A (Figure 1) is retrieved from the Protein Data Bank (PDB).

MarvinSketch

MarvinSketch is an advanced, Java based chemical editor for drawing chemical structures, queries and reactions which supports wide range of file types MOL, MOL2, SDF, RXN, RDF (V2000/V3000), SMILES, SMARTS/SMIRKS, MRV, InChI, CML, PDB etc.

Sketching structures of tripeptides VPP and IPP

Tripeptides (Figures 2a and b) Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) have been drawn using MarvinSketch in MOL format and converted to PDB format using MolConverter.

Molecular docking

Binding of a small molecule (ligand) with a large molecule (protein) is called docking. Docking is the process by which two molecules fit together in 3D space. The objective of computational docking is to determine how two molecules will interact which will aid the interaction studies in bio-molecules. Molecular docking is often employed to aid in determining how a particular drug lead will interact to form a binding pocket.

Patchdock

Patchdock algorithm (Duhovny et al., 2002) is inspired by object recognition and image segmentation techniques that are used in computer vision. Given two molecules, their surfaces are divided into patches according to the surface shape. All possible patches concave, convex or flat surface patches (Figure 3) which can be visually seen are detected using segmentation algorithm. The patches are then filtered, so that only patches with hot spot residues are retained.

Once the patches are identified, they are superimposed using shape matching algorithm. Shape matching algorithm uses hybrid of the geometric hashing (Schneidman et al., 2003) and pose clustering matching techniques to match the patches detected by segmentation algorithm. Concave patches are matched with convex patches and flat patches with any type of patches to obtain complexes. All the candidate possible complexes are examined.
Complexes with unacceptable penetrations of the atoms of the receptor to the atoms of the ligand are discarded. Remaining candidate complexes are ranked according to a geometric shape complementarity score.

**RESULTS AND DISCUSSION**

The output of PatchDock is a list of candidate complexes between receptor (ACE) and ligand VPP (Figure 4) and IPP (Figure 5) molecules. The list is presented in the format of a table. Each table line represents one candidate complex. Solution No. represents the number of the solution. Score correspond to geometric shape complementarity score (Duhovny et al., 2002). The solutions are sorted according to this score. Area stands for the approximate interface area of the complex. ACE indicates Atomic Contact Energy (Zhang et al., 1997). Transformations represented are 3D transformations that include 3 rotational angles and 3 translational parameters. These transformations are applied on the ligand molecule. PDB file of the complex denotes the predicted complex structure in PDB format. High scoring solution structure of ACE-VPP and ACE-IPP are downloaded.

**ACE-VPP and ACE-IPP complexes**

ACE-VPP complex structure (Figure 6a) has a complementarity score value of 4674 with an Atomic Contact Energy (ACE) of 262.56. Closer view of VPP inside the binding pocket of ACE is shown in Figure 6b. ACE-IPP complex structure (Figure 7a) has a complementarity score value
Figure 4. Candidate complexes of ACE – VPP.

Figure 5. Candidate complexes of ACE – IPP.
of 5092 with an Atomic Contact Energy (ACE) of 147.73. Closer view of IPP inside the binding pocket of ACE is shown in Figure 7b.

Conclusion

Enzyme-inhibitor docking is performed between angiotensin I converting enzyme ACE and two natural inhibitors, tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) using the Patchdock Software. Prediction of the intermolecular complex where drug binds to the receptor thereby altering the chemical behavior of the receptor macro-molecule is of vital importance for the analysis of the therapeutics. The docking study provides a quantitative energetic measure that ensures that the tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) are able to inhibit the activity of the ACE which in turn can induce decreased formation of Angiotensin II and decreased inactivation of bradykinin thereby can alleviate HAPE.
Dairy peptides VPP and IPP are small peptides that are formed when casein (milk protein) is broken down into smaller pieces. They can be manufactured using a naturally obtained enzyme preparation to break casein down into hydrolyzed casein powder. They can also be made by fermentation using lactic acid bacteria instead of an enzyme preparation and can be used to inhibit ACE which in turn can alleviate HAPE.

REFERENCES


