J. Chosun Natural Sci.
Vol. 10, No. 2 (2017) pp. 74 – 77
https://doi.org/10.13160/ricns.2017.10.2.74

Protein-protein Interaction Analysis of Bradykinin Receptor B2 with Bradykinin and Kallidin

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Abstract

Bradykinin receptor B2 (B2R) is a GPCR protein which binds with the inflammatory mediator hormone bradkynin. Kallidin, a decapeptide, also signals through this receptor. B2R is crucial in the cross-talk between renin-angiotensin system (RAS) and the kinin-kallikrein system (KKS) and in many processes including vasodilation, edema, smooth muscle spasm and pain fiber stimulation. Thus the structural study of the receptor becomes important. We have predicted the peptide structures of Bradykinin and Kallidin from their amino acid sequences and the structures were docked with the receptor structure. The results obtained from protein-protein docking could be helpful in studying the B2R structural features and in the pathophysiology in various diseases related to it.

Keywords: Bradykinin B2 Receptor, GPCR, Bradykinin, Kallidin, Peptide Modeling, Protein-Protein Docking

1. Introduction

Bradykinin is an inflammatory peptide, consisting of nine amino acids. It involves in the contraction of the venous smooth muscle, activation of sensory fibers, release of cytokines, proliferation of connective tissue and in the endothelium-dependent vasodilation[1,2]. Kallidin, a bioactive kinin, is a decapeptide, having ten amino acids. It is identical to bradykinin with an extra lysine residue added at the N-terminal end. Similar to bradykinin, it also signals through the bradykinin receptors[3].

Bradykinin receptors are rhodopsin-like G-protein coupled receptor family which are highly expressed in the peripheral tissues. They are classified into two subtypes: B1 and B2[4]. One of the bradykinin receptors, B2, is the predominant among the two. It is constitutively and ubiquitously expressed in healthy tissues. The receptor is coupled to G_q and G_i, in which G_q stimulates phospholipase C to increase intracellular free calcium and G_i helps in inhibiting the adenylate cyclase. Also, the receptor stimulates the mitogen-activated protein kinase pathways[4,5]. B2 receptor involves in the slow contraction of various smooth muscles including veins, intestine, uterus, trachea, and lung. It induces the endothelium-dependent relaxation of arteries and arterioles. B2R also activates the natriuresis/diuresis in the kidney[6]. It also mediates the induction and maintenance of cytokine-induced hyperalgesia, along with B1 receptor[7]. It forms a complex with angiotensin converting enzyme (ACE) which is thought to play a role in cross-talk between the renin-angiotensin system (RAS) and the kinin-kallikrein system (KKS)[8,9].

As B2 receptor influences the various processes, starting from muscle contraction to MAPK pathway, it is plausible to consider them as a potential target for treatment of the conditions related to them. Exploring the structural features of B2 receptor thus becomes necessary. We have modeled the receptor using homology modeling and selected best model based on various validation techniques, in a previous study[10]. In this study, we have predicted the peptide structures of Bradykinin and Kallidin, and performed protein–protein docking with the selelcted model of B2R. The docking results could provide the important structural features required to understand the pathophysiology of various diseases related to it.

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(Received : May 8, 2017, Revised : June 16, 2017, Accepted : June 25, 2017)

2. Material and Methods

2.1. Peptide Structure Prediction

The amino acid sequence of the human bradykinin (PubChem CID: 439201) and kallidin (PubChem CID: 5311111) were retrieved from the PubChem database. PEP-FOLD3, a peptide structure modelling platform[11], was used to predict the three dimensional structures of human bradykinin and kallidin peptides. PEP-FOLD is a de novo method, which predicts peptide structures from amino acid sequences. It is based on a greedy algorithm and a coarse-grained force field. PEP-FOLD3 is the recent version of PEP-FOLD which is based on a new Hidden Markov Model sub-optimal conformation sampling approach[12]. Models predicted using the server was used for further docking.

2.2. Protein-Protein Docking

To perform protein-protein docking of B2R with the peptides, ClusPro 2.0, a protein-protein docking server was used[13,14]. ClusPro is identified as the best web server to perform protein-protein docking and has performed well in the critical assessment of prediction of interactions (CAPRI)[15,16]. ClusPro works on a correlation method known as PIPER[17] which calculates the docked conformation energy in a grid using fast Fourier transform (FFT) coupled with pairwise interaction potentials. As a result of the more accurate pairwise interaction potential of PIPER, much fewer near-native structures were only retained. The structures were clustered based on the pairwise RMSD as the distance measure and were optimized.

3. Results and Discussion

3.1. Peptide Structure Prediction

PEP-FOLD3 has generated number of clusters of peptide structures for both the peptides. For bradykinin 23 clusters were developed and for kallidin 34 clusters were generated. After predicting the local structural profile of each of the generated structures, the models were ranked. The best models based on the rank were selected for the further study. The selected models were represented in Fig. 1.

3.2. Protein-Protein Docking

We have performed protein-protein docking of B2R-Bradykinin to identify the important residues involved in the interaction of the natural agonist, Bradykinin, with the receptor B2R. CLUSPRO 2.0 server was used to do protein-protein docking, and 5 different clusters of docked complexes were generated. The top cluster consists of 438 members, and lowest energy weighted score was -982.2. The top cluster was chosen was studying the interaction between the receptor and the ligand. We have identified the important residues involved in the interaction. Protein-protein docking of B2R-Kallidin was performed and 4 clusters of docked complexes were generated. The top cluster consists of 316 members, and lowest energy weighted score was -1025.8. From the docking results, we identified that residues Gln49, Glu51, Trp52, Leu 277, Ile281, Cys282, Ser323, Tyr322 and Cys326 were forming H bond interaction with the peptide. The cluster scores are represented in the Table 1. Fig. 2 Represent the binding mode of both peptides with the receptor.

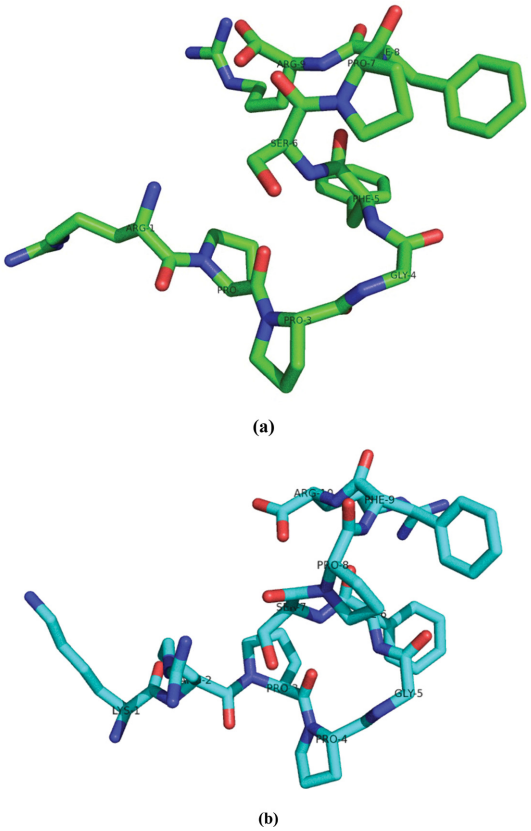
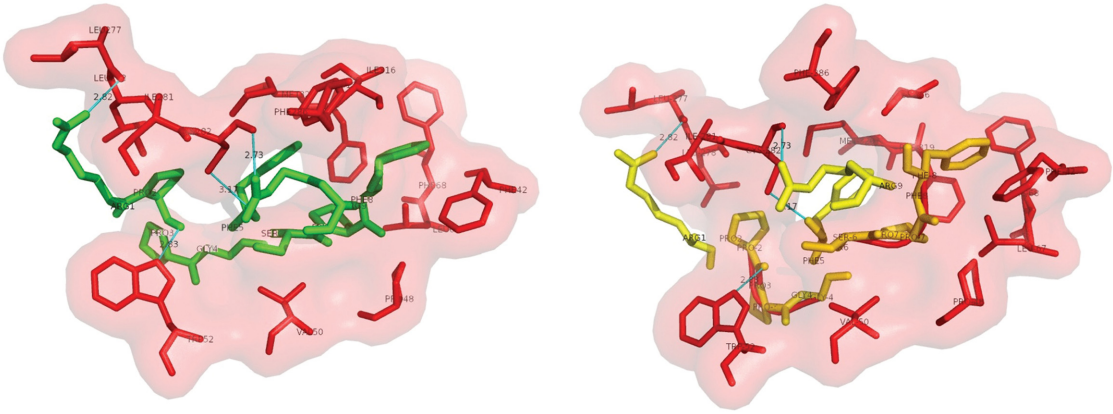


Fig. 1. Peptide structures selected (a) Bradykinin and (b) Kallidin.



(a) (b)

Fig. 2. (a) Binding mode of the native agonist Bradykinin (green) with the receptor B2R (red). (b) Binding mode of the Kallidin (yellow) with the receptor B2R(red). H bonds along with their length are represented as blue lines.

Table 1. Cluster Scores developed using ClusPro server

B2R-Bradykinin docking			
Cluster	Members	Representative	Weighted Score
0	438	Center	-877.3
		Lowest Energy	-982.2
1	202	Center	-876.2
		Lowest Energy	-955.7
2	147	Center	-873.0
		Lowest Energy	-970.2
3	104	Center	-876.3
		Lowest Energy	-948.6
4	97	Center	-870.1
		Lowest Energy	-944.5
5	8	Center	-868.4
		Lowest Energy	-898.1
B2R-Kallidin docking			
Cluster	Members	Representative	Weighted Score
0	316	Center	-941.0
		Lowest Energy	-1025.8
1	264	Center	-911.8
		Lowest Energy	-1072.3
2	258	Center	-914.7
		Lowest Energy	-1052.9
3	131	Center	-916.3
		Lowest Energy	-1009.4
4	29	Center	-914.0
		Lowest Energy	-961.9

4. Conclusion

Three dimensional models for peptides Bradykinin and Kallidin were generated using the PEPFOLD3 web server. Best models were selected, by ranking them based on their local structure profiles. The selected was then docked with a model of Bradykinin receptor B2 using Cluspro online server. The resultant docked complex identified the crucial residues involved in the receptor-ligand complex formation.

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