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Protein–Protein Interaction Analysis of KiSS1–Derived Peptide Receptor with Kisspeptin–10 and Kisspeptin–15

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Abstract

KiSS1-derived peptide receptor, a GPCR protein, binds with the hormone Kisspeptin plays a major role in the neuroendocrine regulation of reproduction. It is important in the onset of puberty and triggers the release of gonadotrophin-releasing hormone. It is a potential drug target for the disorders related to GnRH, hence, analysing the structural features of the receptor becomes important. The three dimensional of the receptor modelled in a previous study was utilised. In this study, we have analysed the protein – protein interaction of the receptor with Kisspeptin 10 and 15. The study revealed the important residues which are involved in the interaction. The result of this study could be helpful in understanding the mechanism of Kiss1 receptor activation and the pathophysiology of the disorders related to the receptor.

Keywords: KiSS1-Derived Peptide Receptor, GPCR, Kisspeptin, Metastin, Protein-Protein Docking.

1. Introduction

KiSS1-derived peptide receptor (GPR54), one of the G-protein coupled receptors[1,2] are activated by the peptide hormone kisspeptin (metastin). Kisspeptin (or metastin) is encoded by the Kiss-1 gene[3], which was initially considered to be a metastasis inhibitor[4], found to be playing a crcuial role in the neuroendocrine regulation of reproduction[5] and in the secretion of gonadotrophin-releasing hormone (GnRH)[6]. Shahab et al., suggests that the onset of puberty could be the result of an increased hypothalamic GPR54 signalling[7]. The suggestion was supported by Seminara et al., in their study, which suggests that by inactivating mutations in the gene that encodes for GPR54, a pubertal delay in human could be caused[8]. In a study by Funes S et al., developmental abnormalities in both male and female genitalia of a mutant mouse line with a targeted disruption of the GPR54 receptor was seen. The study also report histo-pathological changes in tissues which contained sexually dimorphic features[9]. Though GPR54 and metastin are expressed in various other tissues and their functions have not been clearly reported. The immune-reactivity of kisspeptin is found to be expressed in elevated level during human pregnancy, which is reported in a study by Horikoshi et al.[10]. Also, they are identified to be a potent vasoconstrictor in humans, which reports their crucial role in the cardiovascular system[11]. In hippocampal dentate granule cells, kisspeptin controls the synaptic excitability[12] and controls insulin secretion in the islets[13]. Thus, it becomes important to study the structural features of kisspeptin and GPR54. In a previous study, we have modelled the 3D structures of GPR54 using homology modelling[14]. In this study we have modelled the 3D structures of Kisspeptin–10 and Kisspeptin–15 using homology modeling, and performed protein-protein docking of the selected models with the models of GPR54. The important residues involved in the interaction were identified. The result of this study could be helpful on the analysis of structural features and binding features of kisspeptin/GPR54 interaction.

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2. Material and Methods

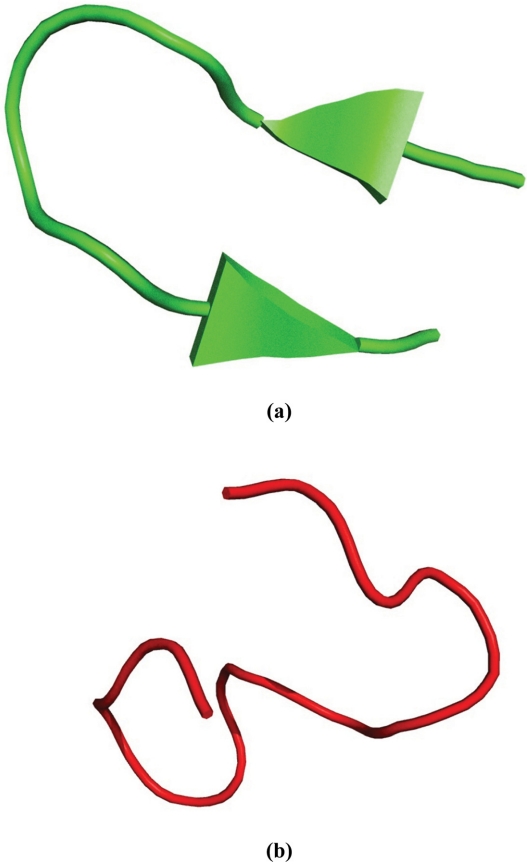
2.1. Homology Modelling

The amino acid sequence of the human kisspeptin-10 and kisspeptin-15 were retrieved from the PubChem database: accession numbers 25240297 and 135652242

respectively. The modelling platform, PEPFOLD-3, an online server using a de novo approach to predict peptide structures from amino acid sequences[15], was utilised to model the 3D structures of human kisspeptin-10 and kisspeptin-15. One best model for each protein was selected and was used for the study.

2.2. Protein-Protein Docking

To perform protein-protein docking of kisspeptin-10 and kisspeptin-15 with GPR54, ClusPro 2.0, the best web server to perform protein-protein docking, server was used[16,17]. It has performed well in the critical assessment of prediction of interactions (CAPRI)[18,19]. PIPER, a correlation method[20] identifies the docked conformation energy in a grid. The structures were clustered based on the pairwise RMSD as the distance measure and were optimized.



(a)

(b)

Fig. 1. Peptide structures selected (a) Kisspeptin-10, (b) Kisspeptin-15.

3. Results and Discussion

3.1. Peptide Structure Prediction

PEP-FOLD3 generated number of clusters of peptide structures for both the peptides. For kisspeptin-10, 6 clusters were developed and for kispeptin-15, 34 clusters were generated. After the models were ranked by predicting the local structural profile of each of the generated structures, best models based on the rank were selected for the further study. The selected models were represented in Fig. 1.

Table 1. Cluster scores developed using ClusPro server

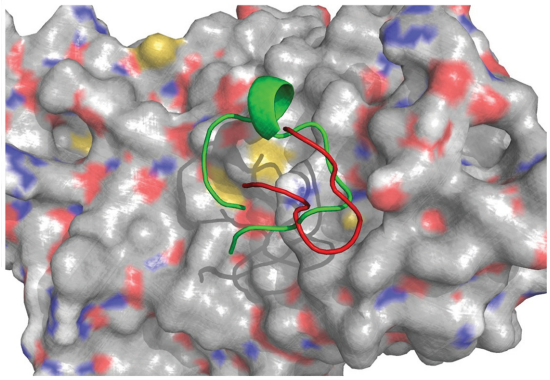
KissPeptin10			
Cluster	Members	Representative	Weighted Score
0	235	Center	-960.7
		Lowest Energy	-1003.3
1	196	Center	-971.9
		Lowest Energy	-1035.7
2	174	Center	-850.2
		Lowest Energy	-951.4
3	110	Center	-891.2
		Lowest Energy	-905.2
4	99	Center	-890.3
		Lowest Energy	-933.3
5	60	Center	-962.3
		Lowest Energy	-962.3
6	45	Center	-858.2
		Lowest Energy	-906.7
7	27	Center	-915.1
		Lowest Energy	-915.1
8	25	Center	-859.5
		Lowest Energy	-894.9
9	13	Center	-857.0
		Lowest Energy	-885.0
10	10	Center	-856.8
		Lowest Energy	-887.3
11	3	Center	-850.2
		Lowest Energy	-855.9
12	2	Center	-852.8
		Lowest Energy	-852.8

Table 1. Continued

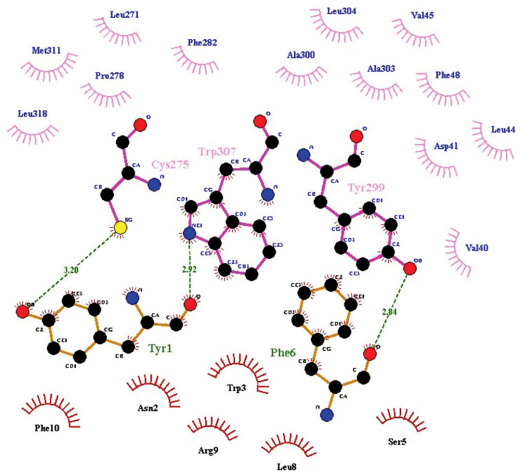
KissPeptin15			
Cluster	Members	Representative	Weighted Score
0	170	Center	-749.7
		Lowest Energy	-878.0
1	143	Center	-785.0
		Lowest Energy	-845.5
2	134	Center	-747.7
		Lowest Energy	-830.8
3	131	Center	-750.9
		Lowest Energy	-834.2
4	111	Center	-762.4
		Lowest Energy	-820.0
5	92	Center	-753.6
		Lowest Energy	-816.9
6	69	Center	-773.2
		Lowest Energy	-864.4
7	53	Center	-826.6
		Lowest Energy	-842.4
8	47	Center	-811.0
		Lowest Energy	-811.0
9	28	Center	-761.6
		Lowest Energy	-769.3
10	19	Center	-780.4
		Lowest Energy	-803.2

3.2. Protein-Protein Docking

CLUSPRO 2.0 server was used to perform protein-protein docking to identify the important residues involved in the interaction. For GPR54-kisspeptin-10 complex, 12 different clusters of docked complexes were generated. The top cluster consists of 235 members, and lowest energy weighted score was -1003.3. 10 different clusters of docked complexes were generated for GPR54-kisspeptin-15 complex and the top cluster consists of 170 members, and lowest energy weighted score was -878.0. On analysing the complexes, we have identified that residues CYS275, TYR299, ALA300 and TRP307 were forming H bond interaction with the peptides. The cluster scores for both the complexes are represented in Table 1. The binding mode of both peptides with the receptor and their corresponding LigPlot are represented in Fig. 2.



(a)



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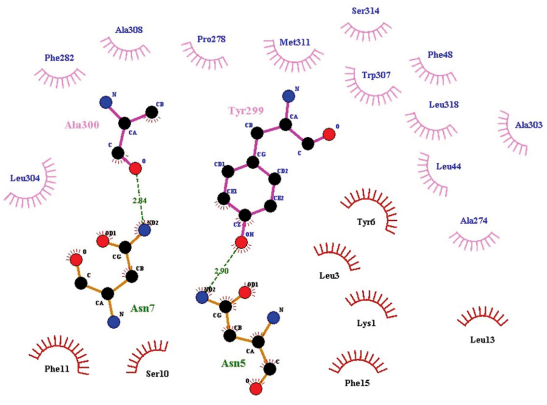

(c)

Fig. 2. (a) Binding mode of Kisspetin-10 (green) and kisspetin-15 (red) with the receptor GPR54. (b) LigPlot of Kisspeptin-10 and GPR54 complex. (c) LigPlot of Kisspeptin-15 and GPR54 complex.

4. Conclusion

3D models of Kisspeptin-10 and -15 were developed using the PEPFOLD3 server and best models were selected based on their local structure profiles. The selected models were then docked with the model of GPR54 receptor using Cluspro online server. On analysing the docked complexes, we have identified the crucial residues involved in the receptor-ligand complex formation.

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