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In silico docking analysis of newly formulated agonist, Ammonio Cyclopentyl Sulfonate (ACS) for human Metabotropic Glutamate Receptor 7 (GRM7) and its drug likeliness properties.

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ABSTRACT

Glutamate is the most abundant neurotransmitter in the central nervous system and metabotropic glutamate receptor 7(GRM7) play a vital role in the mediation of excitatory neurotransmission. Any impairment in GRM7 may lead to many neurodisorders like Parkinson's disease, Alzheimer's disease and epilepsy. In this study we analyzed the 3D structure of GRM7 and developed a new agonist Ammonio Cyclopentyl Sulfonate (ACS) which will enhance its activity. Also we demonstrated the binding affinity of ACS towards GRM7. Drug likeliness property of ACS was also evaluated. Our results suggest ACS can be used as an agonist to treat neurodisorders thereby act as a neuroprotective agent.

KEYWORDS

Glutamate;
Metabolic neuro disorders;
Metabotropic glutamate receptors;
GRM7;
Agonist;
Neurotransmission;
Drug likeliness;
Neuro-protectant.

INTRODUCTION

Glutamate is the major neurotransmitter in the central nervous system. Its function is mainly mediated by the metabotropic glutamate receptors. Metabotropic glutamate receptors are of three types where group III includes metabotropic glutamate receptor 7 (GRM7 or mGluR7) (1). mGluRs are believed to be the key molecule in cognitive functions such as learning and memory. Glutamate receptors mGluRs involves in a number of intracellular signaling pathways. It acts by activating the phospholipase C and suppressing the adenylate cyclase thereby mediating the excitatory neurotransmission (2). Impairment in the GRM7 leads to uncoupling of glutamate, which leads to many neurological disorders such as epilepsy, Parkinson's disease, Alzheimer's disease, depression, mood disorders, anxiety (**3**). Apart from binding of glutamate with GRM7, calcium (Ca^{+}) binds with the GRM7 to form GRM7-Ca^{+}-calmodulin complex through the phosphorylation of protein kinase C. GRM7 mediated neurotransmission depends on association molecules such as enzymes, scaffold proteins, synaptic anchor proteins (4). Lot mutations have been reported in GRM7, rs6443074 and rs329037 are few mutations that were reported in neurotransmission systems gene and bipolar disorder (5). Besides this, some non

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synonymous mutations have been reported in GRM7 by Hiroki et al. While mGluR group I and group II are studied extensively, due to the lack of pharmacological tools, group III mGluRs are least studied. The recent development of N, N'-dibenzyhydryl-ethane-1, 2-diamine dihydrochloride (AMN082) act as an allosteric agonist for GRM7. Also DCG IV [(2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl) glycine] a general agonist for mGluRs was used as a neuroprotective agent against neuronal ischemia (6,7). Our present study aims to design an effective agonist for GRM7 using *in silico* method. As the three dimensional structure of the protein is necessary for performing the docking studies, we first used homology modeling to create 3D structure of GRM7. Further we performed *in silico* docking technique to analyze the binding affinity of the newly modeled agonist ACS. Also the drug likeliness of the ACS was also identified using computational techniques.

METHODS

The sequence information of the GRM7 was collected from Swissprot server. The sequences were collected in Fasta format. Before performing the homology modeling the collected sequence was run against BLAST search to identify the suitable template. The template used here was the crystal structure of group III metabotropic glutamate receptor 7 of *Rattus norvegicus* (2E4Z) (8).

Homology modeling

For homology modeling, we used Modeller ™ to design the three dimensional structure of GRM7 which uses restraint based technique and gives the 3D structure of the input sequence. Careful attention was given in selecting the template. Using eValue, identities and gaps 2E4Z was selected as a best template (9). Before performing the docking studies the active sites were identified using swisspdb viewer.

Autodock vina™

Docking studies were performed for both DCG IV and ACS using Autodock vina version 4.05 ™ running on HCL computer with Intel Pentium dual core processor (10). We interpreted results based on the dock score and binding affinity of agonist with amino acids in the active site. After docking, the binding affinity, hydrogen bonding and bonding distance of the agonists, including DCG IV and ACS was interpreted using Discovery studio visualizer 2.5 ™ (Accelrys, San Diego, CA).

In silico modeling: Drug likeliness ™

To analyse the binding nature of the agonist, we further preformed the *in silico* identification of drug metabolism. The drug likeliness and the properties of the drug were identified using Molinspiration, an online tool which predicts the drug likeliness and its properties. Drug likeliness was assessed based on Lipinski rule of five (11).

RESULTS AND DISCUSSION

The spatial restraint crystal structure of the GRM7 of *Rattus norvegicus* was used as the template, to model the three dimensional structure of

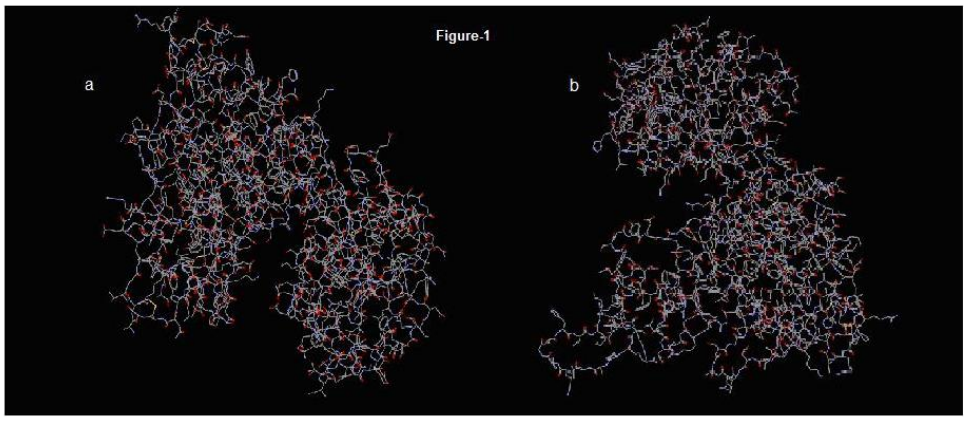

Figure 1 : Explains the modeling profile of GRM 7. (a) Crystal structure of the metabotropic glutamate receptor of Rattus norvegicus; visualized through Discovery studio version 2.5. (b) Predicted three dimensional structure of the human GRM7 using modeller TM software

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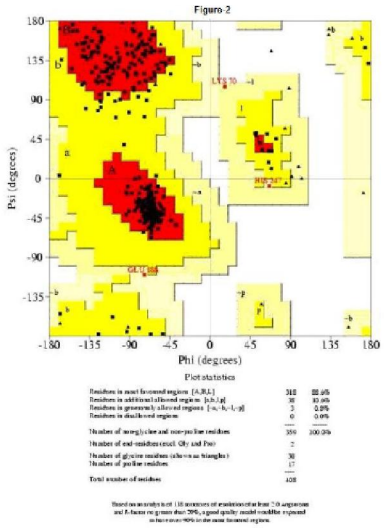
the GRM7 of *Homo sapiens*. Figure 1a indicates the crystal structure of the *Rattus norvegicus* GRM7 and Figure 1 b indicates the predicted three dimensional structure of GRM7 of *Homo sapiens* using Modeller ™. The predicted model was validated using Ramachandran plot from savs server-procheck (12). The results for the protein 3D structure validation is given in Figure 2.

There are no amino acids in the disallowed regions of the Ramachandran plot where 88.6 % of amino acid falls in the most favored region implying the predicted model to be a reliable one. Since DCG IV was generally used as an agonist for group II and III metabotropic receptor, we consider this as a positive control. The structure of the DCG IV was collected from Pubchem database. The details of the DCG IV are given below.

As active site 1 is predicted to be involved in the binding of the glutamate for neurotransmission, we docked DCG IV (control) with the active site 2 of GRM7. After this, ACS (Figure 3 a), the test compound was docked in the active site 2. Autodock vina version 4.05 was used for docking technique. The dock score and the hydrogen bonding potential were analyzed through discovery studio visualizer 2.5 (TABLE 1). The new drug candidate ACS has sulfur atom at position 8. The properties of ACS were identified through molinspiration server and its results were tabulated (TABLE 2).

The hydrogen bonding and binding distance after docking of DCG IV with GRM7 was shown in the Figure 3 b. It possessed only two hydrogen bond interactions as compared with ACS which has 4 interactions as shown in Figure 3 c. From TABLE 1, it can be identified that ACS has more dock score (-6.6) as compared with that of DCG IV which was



Compound ID: 5310979

Molecular weight: 203.14946 [g/mol]

H-bond donor: 4

H-bond acceptor: 7

Figure 2 : Results from ramachandran plot of the human GRM7

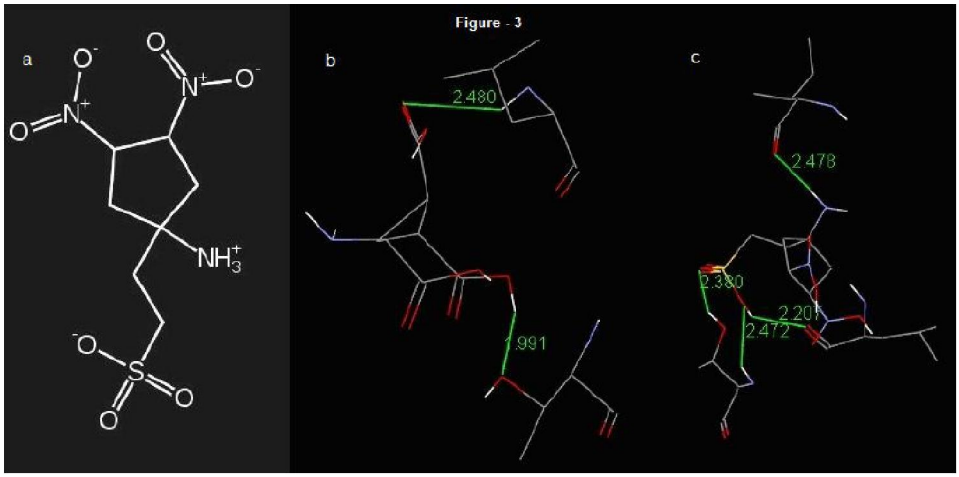


Figure 3 (a) Chemical structure of the ACS, GRM7 agonist. (b) Shows the docking for interaction of DCG IV with GRM7 in active site 1. (c) Binding of ACS with GRM7 in active site 2.

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TABLE 1 : Results for comparitive docking analysis of DCG IV & ACS

Drug candidate	Dock score	Hydrogen bonds	Interactions	Distance
DCG IV	-5.5	2	Leu30	2.480
			Thr32	1.991
ACS	-6.6	4	Thr32	2.472
			Thr32	2.380
			Leu30	2.207
			Ile78	2.478

TABLE 2 : Properties of the newly formulated drug candidate ACS

Name	ACS
IUPAC name	2-{(3S,4S)-1-amino-3,4-bis[hydroxy(oxo)ammonio]cyclopentyl}ethane Sulfonate
Molecular formula	$C_7H_{13}N_3O_7S_1$
Molecular weight	283.259 [g/mol]
mi LogP	-2.921
No. of rotatable bonds	5
No. of atoms	18
No. of violations	0
TPSA	172.041
No. of acceptors	10
No. of donors	3

TABLE 3 : Results for the drug likeliness of ACS using molinspiration server

Drug likeliness	Values
GPCR ligand	-0.51
Ion channel modulator	-0.38
Kinase inhibitor	-1.53
Nuclear receptor ligand	-0.95

only -5.5. The bond distance between ACS and the amino acid present in the active site of the GRM7 was also good. Since drug likeliness depends on the Lipinski rule of five, where the molecular weight of the formulated drug should not exceed more the 500 daltons, logP value should be less than 5, hydrogen bond donors should be less than 5 and hydrogen bond acceptors should be less than 10, (13) careful attention was paid while designing the drug candidate to fit in the rule. After the docking procedure, ACS was analyzed for drug likeliness using Molinspiration server, which is considered as an important descriptor in assigning the bio activity and drug likeliness properties of a compound. Molinspiration uses Bayesian statistics to find out the drug likeliness, the reliability is high as 96.1% (14).

Our results (TABLE 3) showed the values of the ACS to be in the acceptable range. This molecule activity score is generally a number, typically between -3 and 3. As molecules with the highest activity score have the highest probability to be active, our numbers between -3 and 3 were considered to be acceptable thereby supporting the drug likeliness property of ACS.

CONCLUSION

GRM7 is an important member in GPCR protein family which involves in the neurotransmission. Mutation and other conformational changes in the GRM7 may lead to neuro disorders especially epilepsy, Alzheimer's disease and Parkinson's disease. Thus finding a novel agonist for GRM7 becomes essential in disease management. In this work, we modeled the 3D structure of the GRM7 and formulated a new agonist (ACS). ACS showed good docking ability with target. Also the drug likeliness of ACS was good. The above result prove the ability of newly formulated drug candidate as an agonist for treating patients with GRM7 defects and pave the way for future laboratory testing of ACS and its analogs.

REFERENCES

[1] Xia.Li, Eliot.L, Gardner, Zheng Xiong.Xi; Neurop-

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harmacology, **54(3)**, 542–551**(2008)**.
[2] Hiroki Goto et al.; **9**, 224 **(2009)**.
[3] Irina Sinakevitch et al.; **5,** 10 **(2010)**.
[4] Ralf ENZ et al.; Biochem.J., **372**, 183–191 **(2003)**.
[5] Jiajun Shi et al.**; 147B(7), 1270–1277** (**2008).**
[6] H.Yoshioka et al.; Neurosciences Letters, **461**, 266-270 (**2009).**
[7] Z.Fei et al.**;** Journal of clinical Neuroscience, **13**, 1023-1027 **(2006)**
[8] T.Muto et al.; S.Proc.Natl.Acad.Sci.U.S.A., **104(10)**, 3759–3764 **(2007)**.
[9] Nicholas Furnham; BMC Structural Biology, **8**, 7 **(2008)**.
[10] O.Trott, A.J.Olson; Journal of Computational Chemistry, **31**, 455-461 **(2010)**.
[11] C.A.Lipinski; J.Pharmacol Toxicol Methods, **44(1)**, 235-49 **(2000)**.
[12] R.A.Laskowski, M.W.MacArthur, D.S.Moss, J.M.Thornton; J.App.Cryst, **26**, 283-291 **(1993)**.
[13] Varun Khanna et al.; *BMC Bioinformatics*, **10(15),** 10 **(2009)**.
[14] Hrishikesh Mishra et al.; Bioinformation, **3(9)**, 384–388 **(2009)**.