Abstract:

Background: Depressive disorders are major public health concern worldwide. The currently used drugs are associated with low success rate and significant drug related adverse effects. Therefore there is a focus for the development of drugs acting on different targets. As N-methyl-D-aspartate [NMDA] receptors are involved in the pathophysiology of depression, the present study was undertaken to evaluate the affinity of granisetron on glutamate NMDA receptors.

Materials and Methods: Protein sequence of NMDA receptor of Homo sapiens was retrieved from the NCBI database. The three dimensional structure of NMDA receptor was modeled using SWISS MODEL modeling server and RAMPAGE was used to validate the modeled structure. Molecular structures of test drug, granisetron and control drug, ketamine were retrieved from the PubChem. Docking studies was performed using Hex software.

Results: Homology modeled protein structure validation showed about 90.2% of residues in favorable region. Docking results revealed that granisetron showed the energy value of -246.18 which is much acceptable compared to energy values of already proven molecule, ketamine i.e -176.31.

Conclusion: Targeting the NMDA receptor is the new strategy for the depression disorder and ketamine is the proved drug which is used to target the NMDA receptor for the depression. By comparing the energy values this study showed that, granisetron also to be a potent molecule compared with the ketamine. Based on this data further animal studies need to be performed to understand the safety profile of the drug.

Keywords: Antidepressant, NMDA Receptor, Protein Modeling, Docking Studies

Introduction:

Depression is projected to be the second leading cause of death by the year 2020. Existing antidepressant drugs, developed largely within the context of a monoamine hypothesis of mood disorders, recent, large-scale, community-based studies have made us increasingly aware of the limitations on current treatment strategies. These strategies are associated with significantly delayed onset of therapeutic action and a large percentage of treatment-resistant patients. Only one third of patients treated with conventional antidepressants show satisfactory response and many have reported to suffer from numerous drug related side effects. This current unmet medical need provides an impulsion for the development of alternative treatments based on a deeper understanding of the pathophysiology of depression and related disorders.

Affinity of Granisetron for glutamate N-methyl-D-aspartate receptor to evaluate antidepressant activity by Docking studies

Chethan Kumar S¹, Sathisha Aithal², Umakanth N Patil³, Geetha S⁴

¹Research Coordinator, ²Associate Professor, ³Professor, ⁴Post Graduate, Department of Pharmacology, S.S Institute of Medical Sciences and Research Center, Davangere-577005, Karnataka, India

Address Correspondence to :
Dr. Chethan Kumar S
Research Coordinator
S.S.I.M.S. & R.C, Davangere-577005, Karnataka
Email: chethan_kumar@outlook.com
Mob. : +91 9986061616

The N-methyl-D-aspartate receptor (NMDA) subtype of glutamate receptors has been implicated in crucial pathophysiological processes such as schizophrenia, major depression, and post-traumatic stress disorder. There are evidence that involvement of NMDA glutamate receptor in the antidepressant action of certain drugs. Ketamine, a NMDAR antagonist, possesses rapid-acting antidepressant effects in a subset of individuals who had not previously responded to classical monoaminergic-based medications. Granisetron, 5-HT₃ receptor antagonist is currently used for the treatment of emesis. There is no evidence for the antidepressant action of granisetron in animal models. The present study is undertaken to evaluate interaction of granisetron with NMDA receptors taking ketamine as a control. The results of the study may help in future research on antidepressant activity of granisetron.

Methods

Protein sequence of NMDA receptor was retrieved from the NCBI database. Sequence was retrieved in FASTA format and used for further analysis. The modeling of the three dimensional structure of the protein was performed.
by using SWISS-MODEL\textsuperscript{7}, the built model was visualized in molecular visualization software. Structure validation of protein was done using RAMPAGE\textsuperscript{8}, phi-psi torsion angles for all the residues in structure were plotted in the Ramachandran Plot at RAMPAGE.

Structures of ketamine and granisetron were retrieved from PubChem. All the sdf files obtained from the PubChem were converted into pdb files using the Open Babel software. Docking of receptor and drugs were performed using Hex software. The modeled and docked structures were visualized in PyMol software.

Results
The retrieved sequence of NMDA receptor of Homo sapiens for the present study is listed in Table 1. Results of NMDA receptor modeling showed the QMEAN4 score of 0.674 (estimated model reliability between 0-1) taking Glutamate [NMDA] receptor subunit zeta-1 of Rattus norvegicus as a template structure and the similarity is scored as 98.92% (Table 2). The obtained structure is visualized in PyMol. The stereo chemical quality of the predicted models and accuracy of the protein model was evaluated by Ramachandran Map calculations computed with the RAMPAGE and the results showed that the 90.2% residues are in favoured region (Table 3). Energy values of ketamine and granisetron are shown in the Table 4 and binding of ketamine and granisetron with the NMDA receptor in the binding pocket are shown in Figure 1.

Discussion
Homology modeling of NMDA receptor showed the built quality of the structure is acceptable and the stereo chemical quality of the predicted models and residues of the protein model are in favorable region. This shows the accuracy of the model is more reliable. Based on this protein model, docking studies revealed that granisetron has more affinity for NMDA receptor than ketamine taking energy values into the consideration. So granisetron can be considered as the most potent molecule than the control molecule, ketamine.

Conclusion
The glutamate NMDA receptors are in the focus as they are the target of antidepressant action of certain drugs. Many studies proved that targeting the glutamate NMDA receptor, the antidepressant activity can be achieved. This study showed that granisetron perfectly binds in the binding pockets of NMDA receptors and the energy values showed that the affinity of granisetron for NMDA receptors is more than that of proved ketamine.

From these results we can come to the conclusion that, targeting the NMDA receptor is the new approach to assess the antidepressant activity and also it may overcome the delayed onset of therapeutic action and a large percentage of treatment-resistant patients. This data will be useful further to perform the animal studies to know antidepressant activity and other safety profiles of granisetron.

References

Table 1:
<table>
<thead>
<tr>
<th>Source</th>
<th>Accession No</th>
<th>Sequence length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homo sapiens</td>
<td>AAA88096</td>
<td>1233 aa</td>
</tr>
</tbody>
</table>

Table 2:
<table>
<thead>
<tr>
<th>Template PDB ID</th>
<th>Target</th>
<th>Sequence Identity</th>
<th>QMEAN4 Score (0-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Q41</td>
<td>Homo sapiens</td>
<td>98.92%</td>
<td>0.674</td>
</tr>
</tbody>
</table>
Table 3: Results of structure validation using RAMPAGE

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of residues in favoured region</td>
<td>90.2%</td>
</tr>
<tr>
<td>Number of residues in allowed region</td>
<td>8.0%</td>
</tr>
<tr>
<td>Number of residues in outlier region</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Table 4: Docking results showing the energy values

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Energy values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granisetron</td>
<td>-246.18</td>
</tr>
<tr>
<td>Ketamine</td>
<td>-176.31</td>
</tr>
</tbody>
</table>

Figure 1:
Binding of ketamine (A) and granisetron (B) with the NMDA receptor in the binding pocket visualized in PyMol

How to Cite this article:

Funding: Declared none
Conflict of interest: Declared none