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Molecular Docking To Evaluate N-Type Calcium Channel Blockers for Neuropathic Pain

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Abstract

Neuropathic pain often leads to chronic pain and response to painful and/or innocuous stimuli. Inflammatory condition of tissue leads to release of mast cells, T-lymphocytes, macrophages and neutrophils, along with that compounds these cells release numerous compounds that contribute to pain. Recent study shows that immune cells also play a role in neuropathic pain in the periphery. N-type calcium channel blockers a new drug class for the treatment of neuropathic pain. CB2 was first considered as 'peripheral cannabinoid receptor'.CB2 receptor mainly involved in the modulation of inflammatory and neuropathic pain responses.The drug and target interaction were investigated using in-silico docking studies. The in-silico study provides evidence for the interaction of N-type calcium channel blockers with the target proteins namely CB2 receptor. From docking studies it shows an evidence that TROX-1 and cilnidipine provide better efficiency against neuropathic pain. This interaction is presumably vital in exerting the Neuropathic activity. The present study clearly elucidates that N-type calcium channel blockers shows better activity against neuropathic pain.

Keywords: Neuropathic Pain, TROX-1, Cilnidipine, CB2 receptor, Docking

INTRODUCTION

Neuropathic pain (NP) normally characterized as abnormal unpleasant sensation (dysesthesia), increased intensity of response to painful stimuli (hyperalgesia) and pain in response to normally painless stimuli (allodynia). [1]The pathology of the peripheral disorders that cause neuropathic pain involves the small unmyelinated C fibres and the myelinated A fibres, namely, the Aβ and Aδ fibres. Peripheral neuropathic pain commonly affect aged populations due to increased diabetic mellitus, chemotherapy treatment etc, which affect sensory fibers (Aβ, Aδ and C fibres).[2] The common causes of neuropathic pain are toxicity, metabolic disease, trauma, infection, compression, autoimmune diseases, congenital disease. [3] Scientist have developed calcium channel blockersfor the treatment of neurological disorders and chronic pain.[4] Calcium channels cause transmitter to release thus preventing sensory transmission and chronic pain. However, thus the nature of expression controlled by calcium channels and thus it promote the use of blockers for chronic pain. Although spinally delivered state-independent blockers reduce behavioral and spinal hyperexcitability, micro-injection of peptide blockers into brainstem regions mediating descending control of pain reveals complex pro- and antinociceptive roles of calcium channels and could confound usage of blockers via a systemic rout.[4]

The N-type calcium channel serves as attractive target for therapeutic intervention concerning chronic and neuropathic pain conditions.[5] CB2 was first considered to be the 'peripheral cannabinoid receptor'. As CB2 receptor serves as therapeutic target for pain management and immune system modulation without overt psycho activity, due the presence of those receptor in neurons it serves as significant impacton drug discovery. [6]A number of studies have shown that CB_2 is critically involved in the modulation of inflammatory and neuropathic pain responses. Recent studies has focused on the cannabinoid receptor 2 (CB_2), which mostly expressed in non-neuronal immune cells . CB_2 expression is induced in many tissues and cells, including, under inflammatory conditions and has therefore been implicated as a potential therapeutic target for inflammatorydisorders including chronic pain.CB_2 receptor agonists showed good anti-nociceptive effects in several animal models of pain .[7]

MATERIALS AND METHODS

1. Preparation of protein

The three dimensional crystal structure of CB2 receptor (PDB ID 2HFF) was downloaded from the RCSB Protein Data Bank.

2. Preparation of ligand

The chemical structure of the ligands was obtained from PubChem compound database. It was prepared by Chem Bio Draw and MOL SDF format of this ligand was converted to PDBQT file using PyRx tool to generate atomic coordinates.

3. Docking of drugs with selected targets

Molecular docking of N-type calcium channel blockers with CB2 recptors were performed using Autodock[8]. The 3D structure of CB2 receptor (PDB ID 2HFF) was acquired from RCSB (Research Collaboratory for Structural Bioinformatics).

4. Elucidate the binding site

Both Autodock and Vina use rectangular boxes for defining the binding site. The rectangular box centercalculated accordingly from mean of atoms from PyMOL selection and docking box displayed in the PyMOL window.

5. Pilot study

Different trials are performed in molecular docking i.e, Docking with different neuropathic pain receptors are performed and finally selected one receptor in that receptor molecular docking of N- type calcium channel blockers are performed.

6. Software and databases

Two sets of databases are used PubChem and RCBS PDB from these databases protein and ligand molecules are selected. PyRx and PyMOL are the two softwares used for docking thoseSelected compounds.

7. Examination of docking results

Maximum the hydrogen bonding intractions better the docking score . Better the docking score efficiency of the drug is also increased.

8. Molecular docking

Molecular docking is used to recognize and optimize drug candidates by examining and modelling molecular interactions between ligand and target macromolecules. Molecular docking are used to generate multiple ligand conformations and orientations and the most appropriate ones are selected. [9]

RESULTS AND DISCUSSION

Fragment docking

Fragment docking executes quantitative predictions of binding energetic which provide rankings of docked compounds which is based on the binding affinity of ligand-receptor complexes.[10]

Docking studies predict the binding affinity of drug molecule (ligand) into the binding site (receptor)this process is an important part of the structure-based drug design process. Therefore, by the intractions between from the protein/ligand complex thestructural principles are understood, a precise and fast docking and better binding geometries and interactions are required. The docking is done by popular software system such as PyMOL and the molecular docking suites Autodock and Vina and emergehow the brew of docking and magnification can aid structure-based drug design efforts.[11]

Protein crystal structures are processed prior to docking and thus hydrogen atomsare added, hydrogen bonds are optimized, atomic clashes are removed, and other operationsare accomplished that are not part of the x-ray crystal structure refinement process. In addition, ligands must be ready(molecules are downloaded from PubChem)to create 3-dimensional geometries, proper bond orders are assigned , and generate accessible ionization and tautomer states prior to virtual screening.[12] Docked images of N-type calcium channel blockers with CB2 receptors are given below (fig : 1,2,3,4,5,6,7,8)

Chemical structure and molecular formula are given in table .1 Hydrogen bonding intractions between recptor and ligand are given in table .2 Docking score of ligand and receptor are given in table .3

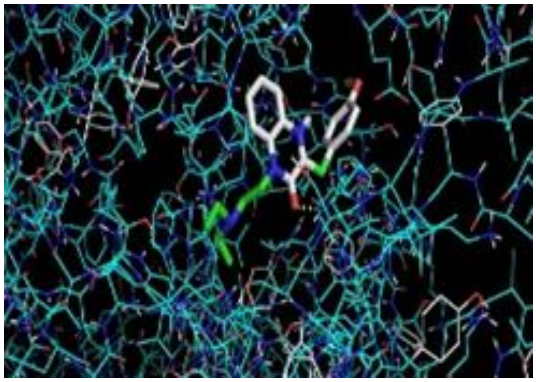


Fig 1.Docked image of caroverine (Ligand) with CB2 receptor(Receptor ID:2HFF)

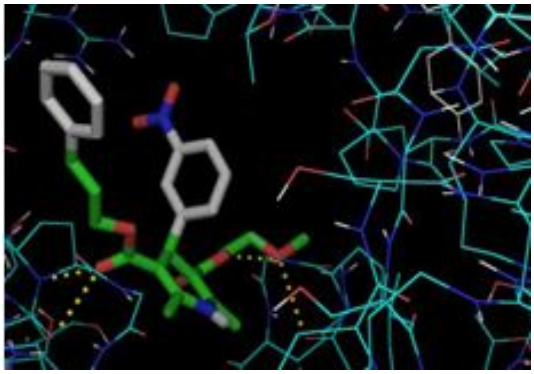


Fig 2.Docked image cilnidipine (Ligand) with CB2 receptor(Receptor ID:2HFF)

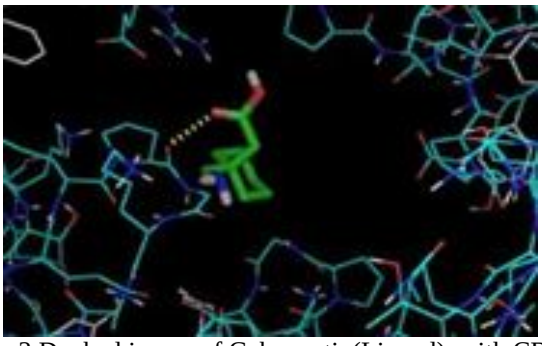


Fig 3.Docked image of Gabapentin(Ligand) with CB2 receptor(Receptor ID:2HFF)

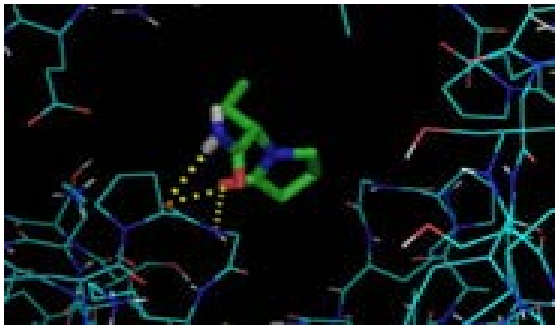


Fig 4.Docked image of Leviteracetam(Ligand) with CB2 receptor(Receptor ID:2HFF)

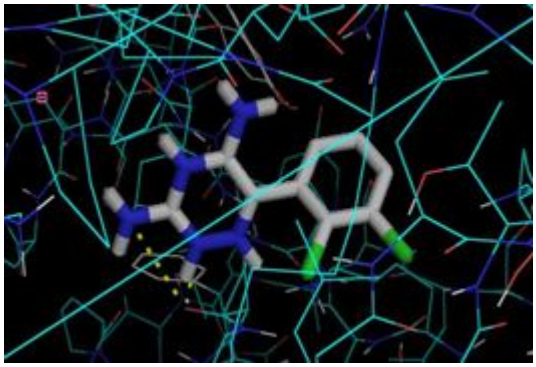


Fig 5.Docked image of Lamotrigine(Ligand) with CB2 receptor(Receptor ID:2HFF)

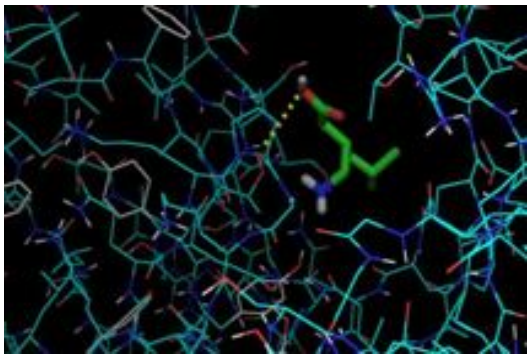


Fig 6.Docked image of Pregabalin(Ligand) with CB2 receptor(Receptor ID:2HFF)

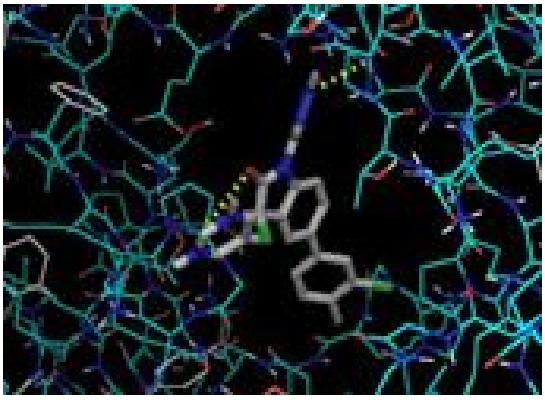


Fig 7.Docked image of TROX-1(Ligand) with CB2 receptor (Receptor ID:2HFF)

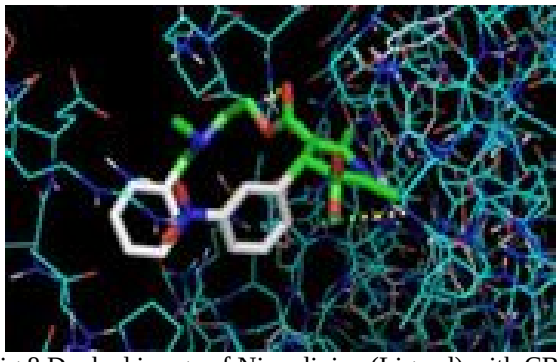


Fig 8.Docked image of Nicardipine (Ligand) with CB2 receptor(Receptor ID:2HFF)

Table .1

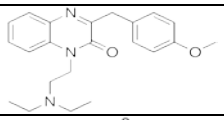
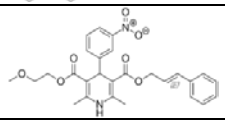
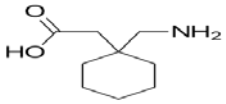
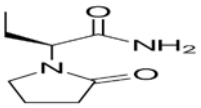
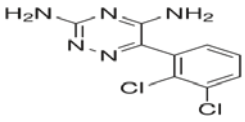
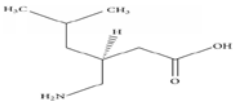
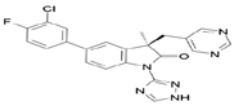
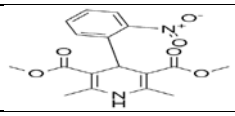
N-type Calcium Blockers	Chemical Structure	Molecular Formula
Caroverine		C22H27N3O2
Cilnidipine		C27H28N2O7
Gabapentin		C9H17NO2
Leveteracetam		C8H14N2O2
Lamotrigine		C9H7Cl2N5
Pregabalin		C8H17NO2
TROX-1		C29H34O17
Nicardipine		C17H18N2O6

Table .2

SL.No	N-type Calcium Blockers	Number Of Hydrogen Bonding Intractions
1	Caroverine	1
2	Cilnidipine	4
3	Gabapentin	1
4	Leveteracetam	3
5	Lamotrigine	2
6	Pregabalin	1
7	TROX-1	2
8	Nicardipine	2

Table.3

SL.No	Ligand and Receptor	Docking Score
1	Caroverine and CB2	-6.8
2	Cilnidipine and CB2	-6.6
3	Gabapentinand CB2	-5.4
4	Leveteracetam and CB2	-5.2
5	Lamotrigineand CB2	-7.0
6	Pregaabalin and CB2	-5.1
7	TROX-1 and CB2	-9.5
8	Nicardipineand CB2	-7.1

CONCLUSION

Docking softwares serves as better choice in finding drug for neuropathic pain. Nowadays neuropathic pain is common among diabetic patients and aged global populations. The study shows that among N-type calcium channel blocking drug TROX-1 shows better binding affinity and cilnidipine shows better hydrogen bonding towards CB2 receptor. Thus, conclude that among N-type calcium channel blocking drugs TROX-1 and cilnidipine provide better pharmacological effect.

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