Computational Screening for Novel Drug Target for Treatment of JME (Juvenile Myoclonic Epilepsy)

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Abstract

JME is a type of epilepsy caused either by inheritance or by some unknown reason. The first line of treatment for this includes drugs like Valproate or a combination of lamotrigine, brivaracetam, and clonazepam, out of which clonazepam is a benzodiazepine. One of its major side effects include drowsiness. We are trying to find novel drugs through computational virtual screening that can target JME without having side effects of current therapeutics which may not be sleep-inducing or do not meddle with a patient's daily routine. We screened many compounds against a target protein mutation from various databases to identify which has the lowest free energy.

Keywords: virtual screening, novel drug target, JME.

Introduction

JME, or Juvenile Myoclonic Epilepsy, is a longstanding disorder of which the main cause has been unknown. Unlike other epileptic episodes, it includes three stages: absence seizure, petit mals, and grand mals. The onset of JME is around the pre-adolescent stage but the symptoms start to show around the age of 15 years. Many research studies have been conducted to find the root cause of JME, but the closest we have gotten to it is by narrowing down the receptors that may be involved in the expression of JME. Some of them are GABA/R(drug target for most benzodiazepines like clonazepam), sodium channels and calcium channels, TRPM2, Myoclonin1/EFHC1 and its mutation like F229L and D210N, etc. The most effective drug to cure JME is Sodium valproate. However, Valproate cannot be administered to girls of childbearing years as it makes them susceptible to having ovarian cysts which in turn causes infertility. We have chosen the protein mutation of EFHC1 i.e., D210N.

Materials and Methods

Software Used: Autodock Vina(downloaded from vina.scripps.edu), Biovia Discovery(for visualization and preparation of protein), Open Babel(for conversion of formats of proteins and ligands), RCSB PDB(protein database), ZINC20(ligand database), Swiss UniProt(protein database for EFHC1).

Methods: We have used protein mutation of EFHC1 I.e, D210N. We further docked seven different compounds: CBD, THC, Mysoline, Valproaic, Taurine, Curcumin, and Gingerol.

Methodology:

First, we downloaded the D210N(PDB ID 5DFJ) protein in PDB format from RCSB PDB, in Human APE1 E96Q/D210N mismatch substrate complex form. Then we downloaded our ligands from zinc.docking.org in an SDF format, which we further converted into the PDB format using Open Babel. Then we prepared the protein using Biovia Discovery, where we removed the unnecessary ligands and chains from it and further created an SBD site sphere at the assumed binding site, where we are supposed to bind our chosen ligand. Then we docked our chosen ligand with our protein in Autodock Vina, where we further extracted them in PDBQT format. We generated the output i.e., a tabulated summary of the calculated free binding energy of each ligand in different torsions.

Result and Discussion

The free energy of interaction between ligands and EFHC1 was found to be -6.4kcal/mol, the lowest for THC. This ligand was interacting with amino acids lysine, arginine and leucine present in the predicted active site(Fig1). After calculating the free energy of every ligand, we then further visualised them and inferred that other than THC no other ligand had any bonding affinity towards chain A possessing an active site.

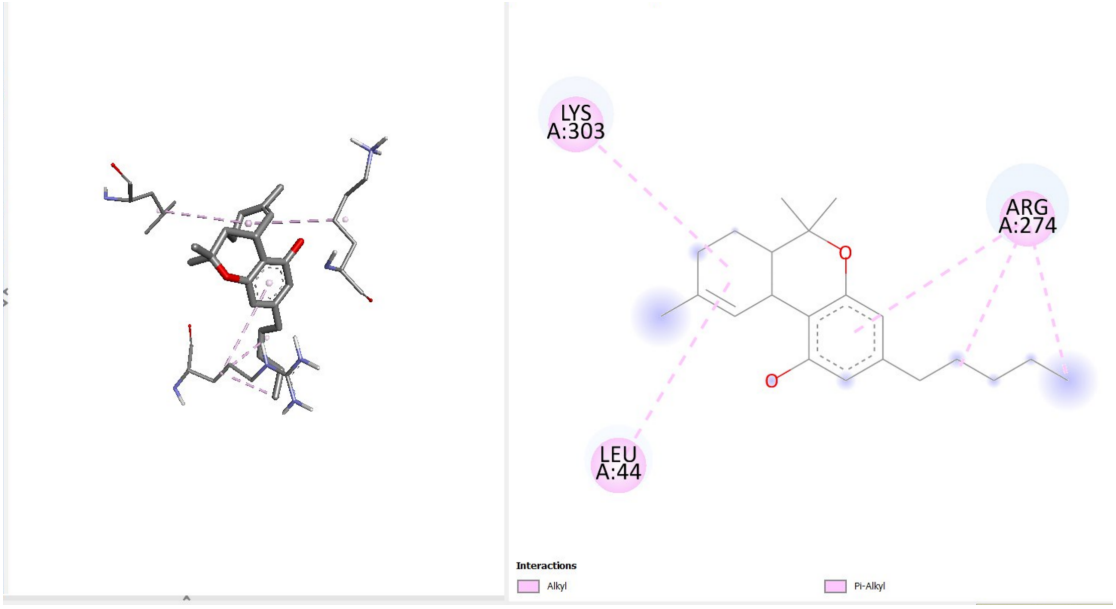

Fig1.shows 3-D structure protein(D210N) and ligand(THC) interaction.
And the 2-D structure shows the ligand interaction with amino acids lysine, arginine and leucine

Conclusion

We have concluded that of all the chosen ligands THC turned out to be the one having the most bonding affinity towards our protein with free energy of -6.4 kcal/mol.

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#################################################################
# If you used AutoDock Vina in your work, please cite:          #
#                                                               #
# O. Trott, A. J. Olson,                                        #
# AutoDock Vina: improving the speed and accuracy of docking    #
# with a new scoring function, efficient optimization and       #
# multithreading, Journal of Computational Chemistry 31 (2010)  #
# 455-461                                                       #
#                                                               #
# DOI 10.1002/jcc.21334                                         #
#                                                               #
# Please see http://vina.scripps.edu for more information.      #
#################################################################

Detected 12 CPUs
WARNING: at low exhaustiveness, it may be impossible to utilize all CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: -89649664
Performing search ... done.
Refining results ... done.

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1         -6.4      0.000      0.000
   2         -6.4      1.230      1.825
   3         -6.3      2.703      6.464
   4         -6.3      2.053      5.719
   5         -6.1      2.090      3.336
   6         -6.1      1.806      2.497
   7         -6.1      2.307      6.316
   8         -6.0      2.499      4.747
   9         -6.0      2.430      4.264
Writing output ... done.
```

Fig2.Shows a log of free energy of ligand THC in different torsions.

References

- Autodock Vina (vina.scripps.edu).
- RCSB PDB (https://www.rcsb.org/structure/5DFJ).
- Biovia Discovery (https://discover.3ds.com/discovery-studio-visualizer-download).
- ZINC20 (https://zinc.docking.org/).
- Open Babel (https://openbabel.org/).
- Epilepsy protein Efhc1/myoclonin1 is expressed in cells with motile cilia but not in neurons or mitotic apparatuses in the brain (Toshimitsu Suzuki1,2, Ikuyo Inoue2 & Kazuhiro Yamakawa1,2).
- The structure of a TRPM2 channel in complex with Ca2+ explains unique gating regulation (Zhe Zhang1,2†*, Bala´ zs To´ th3,4†, Andras Szollosi3,4, Jue Chen1,2, La´ szlo´ Csana´dy3,4*) DOI: https://doi.org/10.7554/eLife.36409.001.
- Mutations of EFHC1, linked to juvenile myoclonic epilepsy, disrupt radial and tangential migrations during brain development (Laurence de Nijs,1,† Nathalie Wolkoff,1,† Bernard Coumans,1 Antonio V. Delgado-Escueta,2 Thierry Grisar,1 and Bernard Lakaye1,*) PMID: 22926142.
- Ligand-induced activation of human TRPM2 requires the terminal ribose of ADPR and involves Arg1433 and Tyr1349 (Ralf Fliegert,1 Joanna M. Watt,2,3 Anja Schöbel,1 Monika D. Rozewitz,1 Christelle Moreau,2 Tanja Kirchberger,1 Mark P. Thomas,2 Wiebke Sick,1 Andrea C. Araujo,1 Angelika Harneit,1 Barry V.L. Potter,2,3 and Andreas H. Guse corresponding author1) PMID: 28515263.