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Molecular Dynamics Simulation of Hyperphosphorylated Tau Protein with Potential Ligands from Drug Repurposing

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Background:

Alzheimer's disease (AD) is the most common cause of dementia. According to Alzheimer's Association, AD is a progressive chronic condition characterized by cognitive dysfunction, including aphasia and agnosia, along with mental symptoms like hallucinations, delusions, and behavioral abnormalities.[1] AD significantly impacts the quality of life for the elderly. The global prevalence of AD is projected to surpass 150 million by 2050, as per the 2022 AD Facts and Figures report.[1] Unfortunately, effective drugs to cure or prevent AD are currently unavailable. Many AD drug discovery research studies have mainly focused on reducing the amyloid plaque load in the brain.[2] This accounts for 70-80% of the drug discovery and development efforts in AD.[2] However, significant limitations and clinical failures relating to amyloid β-based treatments necessitate alternative approaches in developing new therapies for AD. The involvement of hyperphosphorylated tau protein (pTau) in neurofibrillary tangle production in the disease process of AD opens new doors for AD drug discovery. Drug repurposing (repositioning) is a process of discovering a new therapeutic use of existing drugs or drug candidates. It shortens the development cycle and reduces the development costs. In addition, all safety, preclinical and efficacy data are readily available for a repurposed drug. This certainly reduces the failure rate on safety and efficacy during the drug discovery process. This research project aims to investigate if the 3 repurposed drugs, namely asenapine, paliperidone and pentazocine could be repurposed as the pTau aggregation inhibitors by performing molecular dynamics (MD) simulations and analysing the MD simulation results.

Methodology:

MD simulations for all 3 drugs were performed by using AMBER.[3] The initial system configurations for all structures were obtained from the preliminary docking study done by Lim and Yam.[4] Antechamber was used to produce the parameters and coordinates files for accurate representation of all the three ligands.[3] Amber force field FF14SB was used to simulate the pTau, asenapine, paliperidone and pentazocine. On the other hand, the general Amber force field was used to parameterise the ligands.[3] The system was neutralised by chloride ions to achieve a net charge of zero. Following this, the system was solvated into a truncated octahedron TIP3P water box.[3] To remove bad steric clashes and contacts due to solvation, minimisation stage 1 with restraints on the solute and stage 2 without restraints were performed. There were 3 phases of MD simulation, namely heating phase, NVT equilibration phase and NPT production phase.[3] During the heating phase, the temperature of the system was increased from 0K to 300K. The heating phase lasted for 50 ps. Following that, the system was equilibrated for 50 ps under constant temperature (300K) and volume to achieve thermal equilibration and prepare the system for pressure equilibration. Subsequently, NPT production phase lasted for 20 ns. The coordinates were saved for trajectory analysis using CPPTRAJ.[3] All MD simulations were done using the graphics processing unit server, owned by the Swinburne University of Technology, Australia.

Results:

1. Analysis of thermodynamic properties:

All 3 MD simulation systems had stable kinetic, potential and total energies over time. This suggested all systems have reached equilibrium effectively. The stability in energy profiles also indicated that the results from the MD simulations were reliable for analysis. The temperature for all simulation systems maintained around 300K. The pressure, volume and density plots showed all 3 MD simulations were stable.

2. Analysis of structural properties:

2.1 Root mean square deviation (RMSD):

a) RMSD of the entire system:

Asenapine showed the lowest RMSD around 7-10Å, followed by paliperidone's RMSD of 11-14Å and pentazocine's RMSD of 12-16Å. As such, asenapine had a relatively stable interaction with pTau as compared to paliperidone and pentazocine.

b) RMSD of the binding site:

The RMSD of asenapine fluctuated around 1-2Å and this indicated a stable binding. This also signified that asenapine formed a strong and stable interaction with pTau. In contrast, RMSD of pentazocine fluctuated between 1.5-4.5Å while RMSD of paliperidone fluctuated between 1.0-6.5Å. Both pentazocine and paliperidone had higher RMSD values of the binding site which suggested weaker binding as compared to asenapine.

2.2 Root mean square fluctuation (RMSF):

pTau showed large fluctuations around residues 70-80. Similarly, asenapine, pentazocine and paliperidone also showed significant fluctuations around residue 70-80. This finding signified that these regions were highly flexible. The RMSF values of the 3 drugs were generally lower compared to the unbound pTau. This suggested that the presence of 3 ligands made the pTau less flexible. Asenapine demonstrated an overall lowest RMSF trend throughout the MD simulation trajectory. It also showed the most significant stabilization effect in the highly flexible key region (residues 70-90).

2.3 Radius of Gyration (RoG):

The RoG of unbound pTau was 5-9Å. RoG of pentazocine had an overall lowest trend among the 3 drugs and its RoG was 15-17Å. In comparison, RoG of paliperidone was around 15-20Å and its fluctuations were more pronounced. Asenapine showed a RoG between 17-20Å with noticeable fluctuations. The RoG analysis showed that the pentazocine complex was more stable and compact.

2.4 Hydrogen bond (HB) analysis:

Asenapine formed the most stable and frequent hydrogen bonds. It had a total of 46 hydrogen bonds formed. Only 5 hydrogen bonds formed in paliperidone. No hydrogen bond was formed in pentazocine.

Conclusion:

Asenapine appears to be the most promising candidate as a pTau aggregation inhibitor among the 3 investigated drugs due to its stability in both the entire system and at the binding site. It also has the highest number of hydrogen bond formation with the pTau.

References:

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