Asian Journal of Pharmaceutical Technology and Innovation
Abstract

Mechanistic Insights into Interaction of Alzheimer's Drug with Proteins: A Biophysical Approach to Solve Neurodegenerative Diseases

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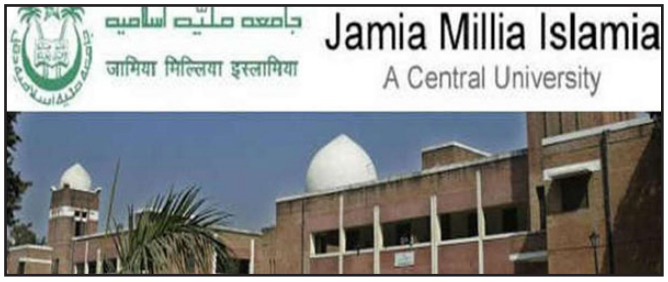
Abstract:

Neurodegenerative diseases affects more than 50 million elderly people worldwide with an associated health care cost of approximately $ 2000 billion per year. Parkinson's disease (PD) and Alzheimer's disease (AD) are linked with high brain iron accumulation relative to the amount of ferritin. Transferrin family is a group of proteins that function in the transport of iron around the blood stream after forming an iron-protein complex. AD is characterized by the presence of amyloid plaques (insoluble deposits of a 4 kDa peptide of ~ 40–42 amino acids in length) which is the leading causes of dementia in humans. Deposition of amyloid plaques is a characteristic feature of Alzheimer's disease and it is this event that leads to neuronal degeneration and cognitive decline. In earlier days, AD was thought of as untreatable condition but with recent advancements, Donepezil, a highly selective and reversible inhibitor, is amongst the widely used drugs for treatment of Alzheimer's disease (AD) across the globe. Clinically significant human transferrin (hTf) is a key player involved in iron metabolism. The current study investigates into the interaction between donepezil and this plasma protein, hTf using UV-vis absorbance, fluorescence, isothermal titration calorimetry, circular dichroism and molecular docking techniques. The mechanism of binding and analysis of conformation of hTf complexed with donepezil were investigated at the molecular level under physiological conditions. Fluorescence spectroscopy clearly revealed occurrence of quenching in the fluorescence intensity of hTf in the presence of donepezil. Measurements of fluorescence at three different temperatures yielded values of binding constant and number of binding sites. Values of binding constant for hTf-donepezil interaction at 303 K and 310 K respectively are 0.007 X 104 M-1 and 1.3 X 104 M-1, implying the strength of this interaction. The negative value of ΔG clearly revealed the formation of hTf-donepezil complex to be spontaneous and thermodynamically favorable. ITC gave an insight into this interaction and showed it to be thermodynamically favorable. Changes in far-UV CD spectrum of hTf in the presence of donepezil further confirmed the complex formation between hTf and donepezil. Molecular docking analysis gave an insight of the specific residues involved in hTf-donepezil interaction. This study gives an insight into the binding of an important Alzheimer's drug, donepezil, with important plasma proteins, thereby giving new prospects and directions to the field of clinical medicine.



Acknowledgements: Asimul Islam acknowledges Jamia Millia Islamia for providing an excellent infrastructure to pursue research. This work was supported by the grants from the Indian Council of Medical Research (ICMR) BIC/12(16)/2014, and Science & Engineering Research Board (SERB), India (SR/FT/LS-48/2010).

Biography:

Asimul Islam is a member of National Academy of Sciences, India (NASI) & his research interest includes Protein Folding, Diseases due to protein misfolding, Macrowmolecular Crowding in Cell, Protein isolation, purification and characterization, Biophysics, Osmolytes and Stress Biology.

Webinar on Nanotechnology and Nanomedicine, August 24, 2020, London, UK

Citation: Asimul Islam; Mechanistic Insights into Interaction of Alzheimer's Drug with Proteins: A Biophysical Approach to Solve Neurodegenerative Diseases, India; Nanomedicine 2020; August 24, 2020; London, UK.