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Full Length Research Paper

Molecular dynamic and monte carlo study on nanoenergetic binding sites of neuraminidase in different media

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Influenza panedemic affect 25 to 30% of the world's population. Neuraminidase (NA) is the most important surfase glycoprotein of the virus causing cleavage of the sialic acid moieties and releasing of newly formed viral particles. The active site of NA is highly conserved all subtype of influaenza virus, then Neuraminidase is the target of drug designs. Using molecular dynamic (MD) and Monte Carlo simulatory methods, the NA structure and its stability different dielcteric (vacuum, water and methanol) and different tempeartures (298, 310, 315, 329 and 333K) was assessed. Measurements of potential energy (Kcal/mol) of binding sites NA in different dielectrics and in different temperatures revealed that at time step size 0 ps, drug binding sites have maximum energy level, and at time step size 100 ps, have minimum energy level and maximum stability.

Key words: Neuraminidase, influenza, molecular dynamic, binding sit, free energy, dielectric.

INTRODUCTION

Influenza, known as flu is a contagious respiratory viral illness of global importance. Individuals at risk of influenza and related complications include older people, young children and individuals with chronic renal, cardiac and respiratory diseases. Influenza viruses are responsible for major devastating worldwide epidemics in the human population. These viruses belong to the Orthomyxoviridae family and can be classified into three types, A, B and C (Arias et al., 2009; Varghese, 1999). Type A is clinically the most important, accounts for all of the human pandemics in the last century: the 1918 H1N1 ‘‘Spanish,” the 1957 H2N2 ‘‘Asian and the 1968 H3N2 ‘‘Hong Kong” and the 1918 influenza pandemic (Nguyen et al., 2011; Wang et al., 2009). Influenza virus can be classified by the antigenic properties of two surface glycoprotein's, hem agglutinin (HA) and neuraminidase (NA) (Shi et al., 2010; Wang et al., 2009) so far 16 subtypes have been identified for HA (H1 to H16) and 9 for the NA (N1 to N9) (Bauer et al., 2009; Margaret et al., 2010; Wang et al., 2009).

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The processes of infected virus

1) Vision enters to host cell by receptor- mediated endocytosis taken into endosome.
2) Low pH allows fusion M2 ion channel makes inside of virus more acidic M1 dissociates and viral.rib nucleoproteins enter nucleus.
3) It pats replication, transcription and translation in host cell till print.
4) mRNAs are synthesis and go to cytoplasm so that it synthesizes protein, then to be in Golgi complex post translation.
5) Nucleoproteins that syntheses (NA, HA and M2) go to surface of host cell (budding) and finally sprout and put

up cell and infect the neighborhood cells (Arias et al., 2009).

Hem agglutinin binds to the sialic acid receptor on the cell surface and facilitates the entry of the virus (Ives et al., 2002; Masukawa et al., 2003). Neuraminidase cleaves the terminal linkage of the sialic acid receptor (Wang et al., 2009). Neuraminidase (NA), also called sialidase is the major surface glycoprotein that possesses enzymatic activity essential for viral replication and infection. NA structure is composed of 4-stranded anti-parallel β-sheets (Margaret et al., 2010; Gong et al., 2007). The active site enzyme is located in a pocket on the surface of glycoprotein. The lipid bilayer containing HA, NA and M2 surround an inner protein layer formed by the matrix protein M1 that encloses the viral genome associated with the nucleoprotein NP and small amounts of PB1, PB2 and PA that form the RNA polymerase complex. Inside the viral particle, it is also the nuclear export protein NEP, also known as nonstructural protein NS2 (Arias et al., 2009). Currently available anti-influenza virus drugs target either the viral M2 ion channel (Amantadine and Rimantadine) or the viral neuraminidase (oseltamivir and zanamivir) (Chien-Yu et al., 2010). In Germany, amantadine, oseltamivir and zanamivir are approved for treating influenza (Bauer et al., 2009); two classes of antiviral agents are currently licensed for the control of influenza infections: M2 ion channel blockers and neuraminidase inhibitors (NAIs). The M2 blockers (Amantadine and Rimantadine) (Margaret et al., 2010; Shi et al., 2010; Bill et al., 2009), Oseltamivir (Tami flu) and zanamivir (Relenza) are currently the only drugs approved for use against types A and B influenza infections (Margaret et al., 2010). Unfortunately, H1N1 virus was reported that it has gained drug resistant for oseltamivir; hence, a new drug is required against this epidemic. For the 1918 influenza NA, there are three crystal structures: 3CYE, 3BEQ and 3B7E (Wang et al., 2009).

The crystal structures of N1 portend a conserved, high affinity calcium binding site located near the active site. The specific role of this calcium in the enzyme mechanism is unclear (Lawrenz et al., 2010). Residues within the active site are highly conserved among all of the NA subtypes including eight charged and polar residues (Arg118, Asp151, Arg152, Arg224, Glu276, Arg292, Arg371 and Tyr406) which have direct interaction with the substrate at the catalytic site. Clinical practices have shown that zanamivir and oseltamivir are effective in treating the 2009 A (H1N1) influenza virus (Xiaojin et al., 2008).

MATERIALS AND METHODS

Homology modeling and molecular dynamic (MD) techniques have been utilized to construct the three-dimensional structure of A (H1N1) neuraminidase. The neuraminidase sequence was collected from the NCBI protein database (2010) and structures were identified as homologous from protein data bank (PDB), enzyme Neuraminidase famous to PDB ID: 3B7E (Xiaojin et al., 2008; Baranovich et al., 2010). The software Argus lab 4.0 drug binding sites were assimilated. Were then simulated with the Monte Carlo (MC); package using the MM+. Their electrostatic potentials were obtained using single-point by the Gaussian 98W program (Frisch et al., 1998). Binding site modes with water box and the four compounds, the overall structure of both complexes appeared to be equilibrated after 100 ps (ΔG binding) binding free energies (ΔG binding) of the four compounds with the neuraminidase of the A(H1N1) virus. The time evolution of the potential energies and the interaction energies are of the four completed systems. There are three steps in carrying out any quantum mechanical calculation in HyperChem 7.0 program package. Firstly, preparing a molecule with an appropriate starting geometry; secondly, choosing a calculation method and its associated (setup menu) options and thirdly, choosing the type of calculation single point, geometry optimization, molecular dynamics, Monte Carlo (MC) vibration options.

The Ramachandran plot of our model shows that 92.0% of residues were found in most favored and additional allowed regions and 8.0% were in the generously allowed region (Wang et al., 2010). The End-Point methods do not include the translational, rotational and conformational entropic contributions but are suitable for drug lead optimization.

RESULTS AND DISCUSSION

This paper studied binding site Neuraminidase in different temperatures and different dielectrics and its most stable models was used in drug design, knowledge of receptor structure in direct theoretical and optimize binding site. Since protein flexibility is important in ligand design, potential energy level lower, stability biding site that is much (Monajjemi et al., 2003, 2006). Amino acids binding with drug include: Asp151, Glu276, Arg152 and Arg371 catalytic site and inhibitor binding the active site are highly conserved among all of the NA subtypes, including eight charged and polar residues (Arg118, Asp151, Arg152, Arg224, Glu276, Arg292, Arg371 and Tyr406) that have direct interaction with the substrate at the catalytic site (Xiaojin et al., 2008). Binding site besides different temperature with step size 100 ps, the first temperature is 298 K since this virus can live in lower temperature so it can be alive in cold seasons and can survive on objects about 2 to 8 h. The second temperature is 310 K (37DC, body temperature), that studied the sites of involved enzyme with drug. The third temperature is 315 (42DC, fever temperature) that studied site involved with drug. The 4 and 5th temperatures are 329 and 333 K selected and studied. As we know dielectric constant are one of the important factors for determining molecule structure and functional biological processes (Monajjemi et al., 2006, 2007). The study of potential energy binding site in different temperatures (298, 310, 315 and 333 K), in ‘vacuum part’ measuring of active enzyme energy NA display that changes in gas part is not meaningful and graphs confirm

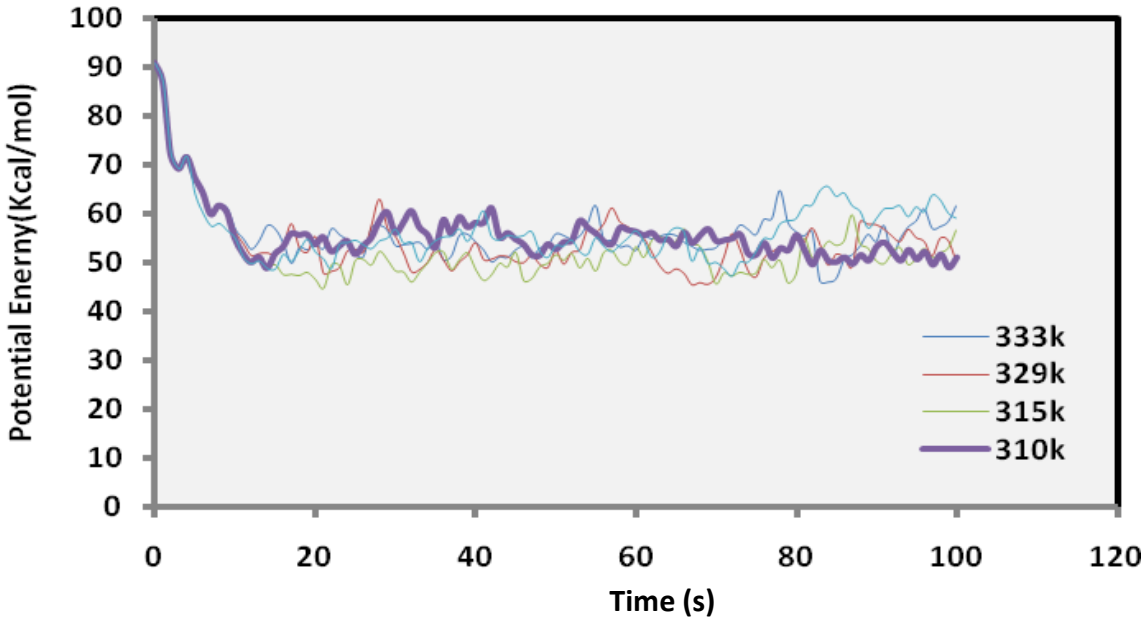

Figure 1. Comparison of potential energy binding site in different temperature in gas part.

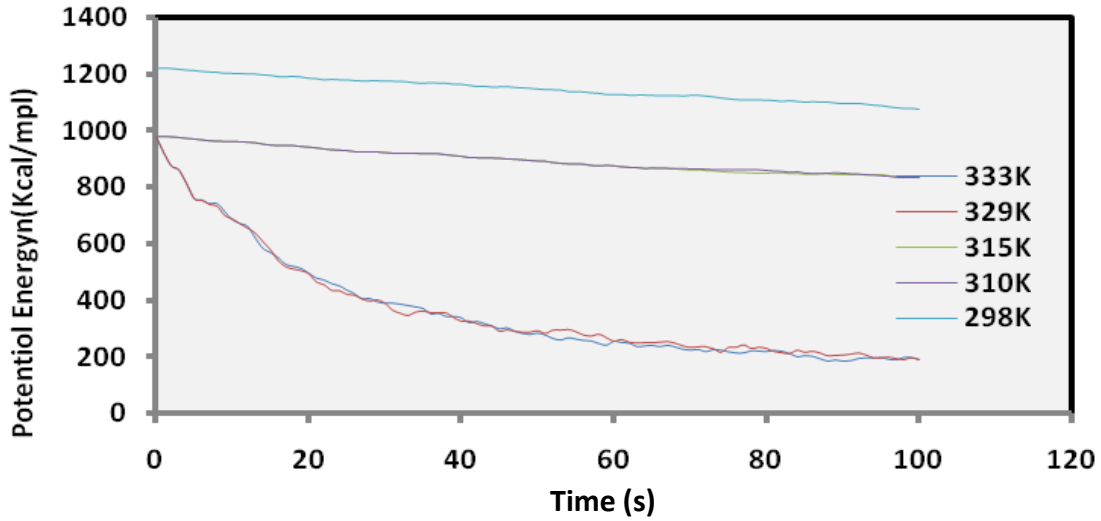

Figure 2. Comparison of potential energy binding site in different temperature in water box.

this results (Figure 1). The study of potential energy in water part that part in binding energy is same way and has the same potential energy of 329 and 333 K have almost had quantity energy and was not observed differently (Figure 2).

The study of potential energy binding site in different temperatures (298, 310, 315, 329 and 333K) in methanol part. Measuring the level of energy from active enzyme NA binding site display that changes energy in watering part. Indifferent temperature, that level of energy in 5 temperatures is quantity and there was no difference in graphs that confirm this note and with spending time it reached the lowest level (Figure 3).

Conclusion

Drug design is mainly based on QSAR (quantitative structure-activity relationship) (Mercader and Pomilio, 2010) knowledge of drug receptor legend and binding is

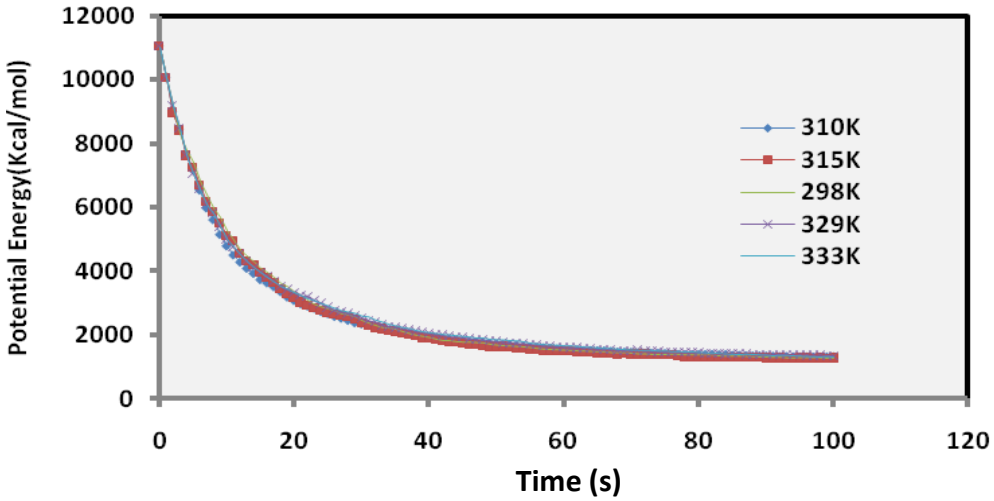

Figure 3. Comparison of potential energy binding site in different temperature in methanol box.

necessary for drug design. Bioinformatics method for drug design is more efficient than previous methods that were based on random screening. In bioinformatics method calculations are rapid and it has low cost rate. Since bioinformatics method is only a part of drug design process, it is necessary that other biological tests should be done on drugs. The active site amino acid is the most interaction with inhibitor is best for drug design. The results reveal that dielectric constants have more influence on binding sites than temperature difference; so the best suitable dielectric is that of water (78.39).

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