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Molecular dynamics simulation study of nerve ion channel

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Abstract

Ion channels are naturally occurring proteins that form hole in membrane. They play multiple roles in many important biological processes. Deletion or alteration of these channels often leads to serious problems in the physiological processes as it controls the flow of ions through it. The proper maintenance of the flow of ions, in turn, is required for normal health. The role of ions channels are now a proved factor behind nerve impulse. Here we have analyzed the nerve ion channel protein, with PDB entry 1BL8, which is basically an ion channel protein in Streptomyces Lividans. The equilibrium energy as well as molecular dynamics simulation is performed first. The possibility of ligand binding is investigated. The change of channel structure is found to be dependent on ligand binding. Implicit water model of the protein is subjected to molecular dynamics simulation to find their energy minimized value. Simulation of the protein in the environment of water and ions has given us important results too.

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Keywords: Ion channels; 1BL8; MD simulation; MC simulation

1. Introduction

Ion channels are proteins that control the passage of ions across cell membranes. They are responsible for such important functions in biological cells as the generation of action potentials in nerves and muscles, the regulation of

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hormone release from endocrine cells [1]. Ion channels have lot of applications as targets for new drugs. They concentrate in biological membranes through which selected inorganic ions pass rapidly. Channels are mainly focused at the central to the function of excitable cells, for example the nervous system and the heart. They are also present in nonexcitable cells and in organisms. Any change in the quality of ion channels induces a number of diseases, for example, the nervous system and the cardiac system. Ion channels consists a major functional class of membrane proteins. Many computational studies can be mentioned where the ion channels are taken up for their research studies [2-9]. In the noble lecture of R. Mackinnon, he explained the structural principles of the gating and regulation of potassium ion channel which governs the electrical signaling in the nervous system with many other physiological processes. [10]. The C-type inactivated K^+ channels serves as water pathway [11]. So it acts for water transport but inhibits ions, though, the importance of water flow. Homology models of the pore loop domain of voltage-gated potassium channels kv1.1-kv1.6 are generated by Liu et al. [12]. Polyamines are identified as the gating molecules of inward-rectifier K^+ channels [13].
Here, the ion channel protein with PDB identity 1BL8 is investigated in different ways. Their structure and ligand binding sites are analyzed. Energy minimization of its structure and MD simulation of the implicit water model and water ion model of the protein are performed.

2. Methods and modeling

The PDB structure of 1BL8 of Streptomyces Lividans are analyzed by Protein Homology/Analogy Recognition Engine V 2.0, Phyre2 [14] from the amino acid sequence. Ligand binding sites are predicted by 3D ligand Site-Ligand Binding Site prediction Server [15]. Binding of ligand is also verified by open source software Abalone.Modeling is done with VMD, Visual Molecular Dynamics software [16, 17] and online simulation CHARMM-GUI [18] are used for energy minimization and MD. For energy minimization hybrid LS and CD method is employed [19, 20]. PyMol is also used for structure visualization.

3. Results and discussion

The protein with PDB name 1BL8 contains 20 aligned regions with 11% disordered region. The detailed structure analysis shows several voltage gated potassium channels in its domain along with membrane protein, transport protein and metal transport potassium channels etc. In the total sequence, 78% alpha helix and 45% transmembrane helix are predicted. Ligand binding site of the protein is found for residue 14, 18, 47, 51 with amino acid LEU, LEU, SER, ALA respectively. The average distances of contact are 0.33 Å, 0.23 Å, 0.29 Å and 0.11 Å respectively. Heterogens are also found in the predicted binding site which is FE, FE2 and ZN with count 6, 11 and 6 respectively. Binding of ligand brings conformational changes. First it opens the channel and then almost deactivates it. The result points towards the sensitization and desensitization of ion channel as found by D.R. Madden [21] in their study. The PDB structure contains four chains and the engineered protein of streptomycin lividans (pore) is shown in Fig 1(a). Fig 1(b) is the topology that the transmembrane helices in this protein sequence are trying to adopt. The four chains in the protein is engineered to form the pore like Fig 1 (c). Ligand binding is also verified by software Abalone. The ligand binding is shown in Fig 1 (d). Metallic heterogens are found in the site of the predicted residue. Structural change on ligand binding is observed here. Binding with ligand will certainly change the nature of ion transport through the channel. So ligand binding should play a crucial role in governing the transport characteristics through the channel.