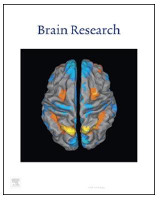
Brain Research 1646 (2016) 560–569

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres



Research report

Effects of electromagnetic field exposure on conduction and concentration of voltage gated calcium channels: A Brownian dynamics study

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ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form
25 May 2016
Accepted 23 June 2016
Available online 23 June 2016

Keywords:
Brownian Dynamics
COMSOL Multiphysics
Voltage gated calcium channel
Electromagnetic radiation

ABSTRACT

A three-dimensional Brownian Dynamics (BD) in combination with electrostatic calculations is employed to specifically study the effects of radiation of high frequency electromagnetic fields on the conduction and concentration profile of calcium ions inside the voltage-gated calcium channels. The electrostatic calculations are performed using COMSOL Multiphysics by considering dielectric interfaces effectively. The simulations are performed for different frequencies and intensities. The simulation results show the variations of conductance, average number of ions and the concentration profiles of ions inside the channels in response to high frequency radiation. The ionic current inside the channel increases in response to high frequency electromagnetic field radiation, and the concentration profiles show that the residency of ions in the channel decreases accordingly.

1. Introduction

There has been a great deal of interest in the past years to study the biological ion channels as the controllers of the cell's electrical activity. These water-filled proteins are embedded in the bilayer phospholipid molecules, and can be the source of disorders in effect of selectively conductive malfunctioning. Hyperkalemic muscle paralysis, muscular and neurological disorders, epilepsy with febrile seizure, polycystic kidney disorders and migraines are all believed to arise from abnormal behavior of Na^+ and Ca^{2+} ion channels (Dolphin, 2000). Based on the vast experimental and computational researches, the understanding of the structure and function of ion channels has progressed enormously. The crystal structure of ion channels has been reported based on experimental measurements (Bass et al., 2002; Doyle et al., 1998; Dutzler et al., 2002, 2003; Long et al., 2005a, 2005b; Unwin, 2005). An important and extremely selective ion channel with high ratio selection is the calcium channel(s). These channels pass 10^6 ions per second and can select between ions of identical radii with a charge selection mechanism. Experimental studies show that in a mixture of calcium with other ions, with a decreasing concentration of calcium ions, the conductance of channel will eventually decrease and then increase. This is the so-called anomalous mole fraction effect (allowing more sodium ions to pass the channel) while there are no more calcium ions present (Almers and McCleskey, 1984). Theoretical and computational methods for solving the complex equations for ion permeation across the channel pores and the mechanisms of ion selectivity have been improved and are playing a significant role.

The first attempts to model the complex ion channel system (channel macromolecules, ions and water molecules) were made with the reaction rate theory (Hille, 2001) which could not, however, relate the structural parameters to the functional elements (McCleskey, 1999). The demonstration of observed properties of the channel structure was made using the Poisson- Nernst-Planck (PNP) theory, based on the continuum electrostatics and electro diffusion equations (Coalson and Kurnikova, 2005; Nonner and Eisenberg, 1998). The shortcomings of this theory were pointed out in different studies (McCleskey, 1999; Miller, 1999). The main drawback comes from the mean-field assumption which ignores the induced surface charges created in the narrow pores in the electrolyte solutions. In order to correlate the channels' structure to its function, ions should be treated explicitly. In molecular dynamics (MD) simulations, pair-wise interactions potential between ions, water molecules, protein molecules and their trajectories are employed but it is not feasible to simulate the entire channel in this way. A number of computational studies and

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http://dx.doi.org/10.1016/j.brainres.2016.06.034
0006-8993/

approaches have been carried out on the structure, the selectivity and the diffusion in the KcsA channel (Allen et al., 2000; Burykin et al., 2003; Noskov et al., 2004).

Brownian dynamics (BD) is computationally affordable to simulate ion permeation in channels and channel conductance and is also in agreement with the experimental observations. This type of modeling with a reduced amount of computations, as compared with the MD, has made BD a distinct method in the simulation of ionic channels. In this technique, the water system is treated as a continuum system and the atoms in the protein ion channel are considered to be fixed. The motion of each ion is tractable via the Langevin equation. The first BD simulations considered one dimensional ion permeation (Cooper et al., 1985) but eventually they were extended to three dimensions with computation of electric fields via the Poisson equation (Li et al., 1998). One of the first models of the L-type calcium channel which was constructed from the experimental properties possess the following main features : a wide extracellular entrance, a narrow selectivity filter (2.8 Å) with four point charges presenting glutamate residues and a long chamber. The narrowness of the channel prevents the ions from passing through each other and also relates the structural features to its function using principles of electrodynamics (Corry et al., 2001). In a recent study the crystal structure and architecture of Orai calcium channel and its selectivity have been identified (Hou et al., 2012). A ring of six glutamate residues around the pore forms the filter on extracellular site. It was indicated that the Ca^{2+} binding site is the extracellular site of glutamate ring and is located within the voltage gradient across the membrane which allows multiple Ca^{2+} selection (Hou et al., 2012). In another model a set of three calcium binding sites cooperate in conductance wherein the selectivity filter oscillates between either one calcium ion bound at the central site or two calcium ions bound at the distal sites (Tang et al., 2014a).

Although no computational work has been reported to cover the application of electromagnetic fields to voltage-gated channels, but in numerous experimental studies the effect of an external electromagnetic field is evident. The 50 Hz pulsed electromagnetic field elevated the intra/ extracellular concentration of calcium ions and also increased calcium channels influx through L-type voltage-gated channel in rat dorsal root ganglion neurons (Li et al., 2014). Several reports have indicated that electromagnetic radiation modifies cellular calcium influx for different frequencies (Wolke et al., 1996; Nazıroğlu et al., 2012; Nazıroglu, 2009). The application of a 50 Hz field increased the calcium current density in a human neuron due to the induced modulation neuronal cell proliferation (Grassi et al., 2004). The inactivation rate and velocity of voltage-gated potassium channel exposed to moderate intensity static magnetic field are altered (Shen et al., 2007) but as for calcium channels no obvious change of current-voltage relationship was found while activation/inactivation, channel currents and intracellular calcium currents were altered (Lu et al., 2015). Extremely low frequency electromagnetic fields seem to induce microvolt potential changes across the membrane (Mathie et al., 2003). Blackman et al. (1988) reported a frequency window as well as a power density window for modulated carrier that enhanced the efflux of the calcium ions in a brain tissue exposed to a frequency of 147 MHz. To understand the signature of the frequency in the calcium ion efflux phenomena, an extended frequency range was tested in the ELF region. No pattern in the frequency response was observed and only certain frequencies were effective in causing enhanced calcium ion efflux but others were not (Blackman et al., 1988).

An experimental study on the spinach cells exposed to static and alternating magnetic fields (60 Hz) with environmentally used amplitudes showed that the calcium channel proteins in the cell membrane were the primary sites of this interaction and that due to the exposure, the calcium efflux through the membrane vesicles increased by 50% from its control value (Sun et al., 2012).

Reviews of twenty three studies show that exposure to an extremely low frequency field, microwave field, static electric field, static magnetic field and nanosecond pulses activates voltage-gated calcium channels and leads to an increase of intracellular calcium ions (Pall, 2013). The exposures are believed to change the electrical voltage gradient across the membrane and therefore stimulate the voltage-gated calcium channel (Radman et al., 2009; Joucla and Yvert, 2012; Minelli et al., 2007).

The aim of this paper is to use the calcium model structure and modify the calculation of electrostatics in a more realistic way using Comsol Multiphysics and BD simulations. The effect of an external electromagnetic field is introduced in the model to study the side effects on the conductance of the ion channel.

Dysfunction of any type of calcium channels will lead to the related diseases such as absence seizures, cerebellar ataxia, familial hemiplegic migraine, Timothy syndrome, autism and many more (Catterall, 2011). The success of our model implies that the atomic structure has a close relation to the parameters of our model, the ionic conductance and occupancy of the selectivity filter is in agreement with the recent findings of calcium channels (Eisenberg, 2010).

2. Results

The voltage-gated calcium channels as the key signal transducers of electrical excitability were studied to investigate and compare the effects of electromagnetic fields on the conduction and concentration of the channel. To get a useful insight into the channel model, a three-dimensional structure of the channel is constructed by rotating the cross section, as depicted in Fig. 1, about the z axis by 180 degree. The channel was enclosed with two cylindrical reservoirs showing the intracellular and extracellular baths. Periodic boundary conditions were employed to keep the ions in the system. To keep the average number of ions in the reservoirs constant, stochastic boundary conditions were applied. The disappearance of an ion from a reservoir had a negligible effect on the ions inside the channel. Electrostatic calculations were required as a prior condition of the simulation.

A driving force was considered by using two plates far away from each other and applying a −120 mV potential difference to them. Fig. 2a shows the resulting potential which affects the channel and the reservoirs. The deviation of the potential variation from a linear behavior is due to the difference in ε (dielectric constant) across the channel and the existence of fixed channel charges. It has been mentioned that the strength and direction of

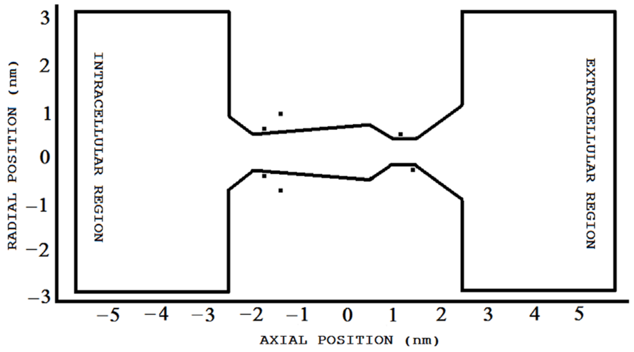

Fig. 1. The calcium channel model and cylindrical reservoirs on either side representing the intracellular and extracellular regions. The point charges are located around the narrow filter region while the dipoles are located near the intracellular mouth region.