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Quantum Tunneling of Ions through the Closed Voltage-Gated Channels of the Biological Membrane: A Mathematical Model and Implications

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Abstract: Voltage-gated channels play an essential role in action potential propagation when their closed gates open, but their role when they are closed needs to be investigated. So, in this study, a quantum mechanical approach using the idea of quantum tunneling was used to calculate the conductance of closed channels for different ions. It was found that the conductance due to quantum tunneling of ions through the closed channels does not affect the resting membrane potential. However, under different circumstances, including change in the mass or the charge of the ion and the residues of the hydrophobic gate, the model of quantum tunneling would be useful to understand and explain several actions, processes, and phenomena in the biological systems.

Keywords: quantum tunneling; voltage-gated channel; quantum biology; membrane potential; sodium ions; potassium ions; lithium ions

1. Introduction

The biological membrane of excitable tissue such as neurons and muscles contains voltage-gated channels such as sodium and potassium channels, which are closed at the resting state of the membrane potential by forming a hydrophobic constriction gate that prevents the permeation of ions by creating a barrier energy higher than their kinetic energy [1–3]. Additionally, voltage-gated channels play an important role in action potential propagation when they get activated and open their gates [1,4]. However, the role of these channels when they are closed at the resting state should be investigated. Here, quantum mechanics offers a reasonable way to investigate the ions' conductance through the closed channels.

Small particles can tunnel through an energy barrier even though their energy is less than the energy of the barrier, this is called quantum tunneling [5]. Many hypotheses have used the idea of quantum tunneling through closed channels in an attempt to understand unexplained phenomena. One of the examples of such bizarre phenomena is referred pain, which has been explained based on the idea of quantum tunneling of potassium ions through the closed channels [3]. Referred pain is important in the clinical practice and can aid in the medical diagnoses [6], so better understanding of the exact mechanism of this phenomenon can enhance the prognosis and the therapeutic outcome for the patients. Furthermore, the quantum tunneling of lithium ions through the closed gate of voltage-gated sodium channels could explain the therapeutic effect of lithium in treating bipolar patients [7]. However, these studies did not focus on the mathematical tunneling model itself and did not give a general picture to be applied on different ions since they focused on special cases.

So, the aim of this study is to set a more accurate and comprehensive mathematical model of quantum tunneling of ions through the closed channels of biological membrane, filling the defects and gaps in the models used in referred pain and the tunneling model of lithium ions, and enhancing the accuracy of their results and implications. The Gamow-type tunneling model is used in the study.

Tunneling calculations become more complicated when moving to two-well potentials. In this case, it is necessary to apply numerical methods to solve the corresponding Schrodinger equation [8,9]. Moreover, by applying the idea of quantum tunneling on the ions, quantum conductance can be calculated and, consequently, the role of closed voltage-gated channels at resting state would be better investigated. In addition, it will serve as a general model to be applied when the issue of quantum tunneling of different ions is addressed to explain different phenomena and understand different pathologies, especially the disorders related to the central and peripheral nervous system such as epilepsy and pain disorders or even to develop new therapeutic agents to treat several diseases.

2. The Mathematical Model of Quantum Tunneling of Ions through the Closed Voltage-Gated Channels

2.1. The Probability of Quantum Tunneling of Ions Through the Closed Channels

Voltage-gated channels such as sodium and potassium voltage-gated channels are sealed off by a hydrophobic gate at the intracellular end of the membrane and this gate blocks the permeation of ions [1–3]. This gate represents an energy barrier that prevents the passage of ions, so the probability of ions tunneling through the gate of closed channels can be calculated by the following equation [5]:

$$T = e^{-2\frac{\sqrt{2m}\int \sqrt{(U-KE)}}{\hbar}}, \quad (1)$$

where T is the probability of tunneling, m is the mass of ion, $\hbar$ is reduced Planck constant, U is the energy of the barrier, and KE is the kinetic energy of the ion.

Each channel needs energy to open the gate so that the ion can pass; this energy represents the total energy of the barrier (hydrophobic gate) that the ion should obtain to go through the channels when the gate is closed. To solve the integral in Equation (1), the hydrophobic gate can be illustrated as an electric field in the space of parallel capacitor that resists the movement of the ions, and its voltage (V) is calculated as $V = \frac{U}{q}$, where U is the energy of the barrier and q is the ion charge. Then, the electric field (E) can be calculated as $E = \frac{V}{L}$, where L is the length of the hydrophobic gate. Eventually, the integral in Equation (1) can be formulated as

$$\int_{X1}^{X2} \sqrt{(qEx - KE)}dx, \quad (2)$$

where $X1$ to $X2$ is the forbidden region where the barrier energy is equal or higher than the kinetic energy: $qEx \geq KE$.

2.2. The Probability of Ions Tunneling Through the Closed Sodium and Potassium Voltage-Gated Channels

There are two main ions that determine the potential of biological membrane as well as the action potential propagation; sodium and potassium ions [1].

Voltage-gated channels are composed of four alpha subunits and each one has six membrane-spanning alpha helices (S1–S6) [10–12]. These channels are closed at resting membrane potential and, thus, they prevent the permeation of the ions. They maintain closed status by forming a hydrophobic gate that is made when four hydrophobic residues from the S6 helices come in close proximity to each other (each S6 helix contributes with one hydrophobic residue of the four ones of the hydrophobic gate) [10,13,14]. It prevents the passage of ions by forming an energy barrier *(U)*, which is higher than the kinetic energy of the moving ions.

The hydrophobic gate has the length of single amino acid residue $D = 1.5 \times 10^{-10}$m [15,16], however, these residues are tilted because the S6 helices form an angle (θ) with the plane of the cell membrane [17,18] (See Figure 1). So, the vertical length (L) must be calculated:

$$L = D \times \sin\theta \tag{3}$$

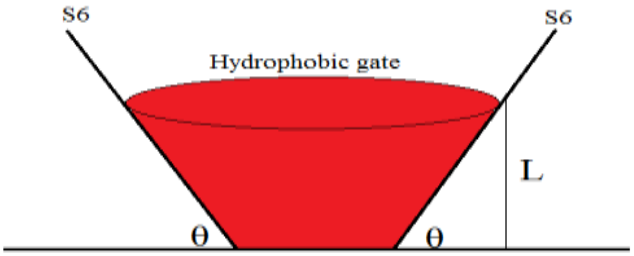

Figure 1. Represents the hydrophobic gate (red in color) made by the constriction of four S6 helices (two of them are represented in the figure for simplicity) of the alpha subunits, the angle θ made by intersection of S6 with the plane of cell membrane, and the vertical length (L) of the gate. (D) represents the hypotenuse of the right-angled triangle made by the vertical side (L), the horizontal side of the cell membrane, and S6 helix of the channel.

The kinetic energy of the ions comes from the voltage difference across the membrane and the concentration gradient. The energy due to the concentration gradient can be estimated by calculating the Nernst potential, which represents the voltage needed to balance the net movement due to the ion gradient, then, it will be used to estimate the equivalent voltage of the ion concentration in the extracellular and intracellular compartments.

The voltage across the membrane for neurons is −90 mV [1] (it is negative inside the neuron in comparison with outside) and this means the positive ions outside will get kinetic energy when they go from outside to the inside across that voltage.

2.2.1. The Tunneling Probability of Sodium Ions

The diffusion potential (Nernst potential) of sodium ions is +61 mV [1]. So, the concentration difference of 128 mEq/L between extracellular sodium 142 mEq/L [1] and intracellular sodium 14 mEq/L [1] needs 61 mV to be balanced. Accordingly, the extracellular sodium concentration is balanced by 67.7 mV, and the intracellular sodium concentration is balanced by 6.7 mV. In addition, the extracellular sodium ions will get additional kinetic energy due to the resting membrane potential (−90 mV). As a result, the extracellular sodium ions have kinetic energy equivalent to 157.7 mV and the intracellular sodium ions have a kinetic energy equivalent to 6.7 mV. By using the following equation, the kinetic energy can be calculated:

$$KE = qV, \tag{4}$$

where KE is the kinetic energy, q is the charge of the ion, and V is the voltage.

So, the kinetic energy for extracellular sodium ions is $KE_{Na(o)} = 2.52 \times 10^{-20}$J, and the kinetic energy for intracellular sodium ions is $KE_{Na(i)} = 0.11 \times 10^{-20}$J.

When tilt angle of alpha helix is 21° [18], $L = 5.4 \times 10^{-11}$m. Besides, the energy *(U)* needed to open the gate of voltage-gated sodium channels is $16.1 Kcal/mole = 11.19 \times 10^{-20}$J [19] and consequently $qE = 2.1 \times 10^{-9}$N.

Regarding the extracellular sodium ions, the forbidden region is from $X_1 = 1.2 \times 10^{-11}$m to $X_2 = 5.4 \times 10^{-11}$m and $\int_{1.2\times10^{-11}}^{5.4\times10^{-11}} (\sqrt{qEx - KE})dx = 8.3 \times 10^{-21}$. As a result, the tunneling probability by applying Equation (1) is $T_{Na(o)} = 1.16 \times 10^{-19}$. On the other hand, the forbidden region for intracellular

sodium ions is from $X_1 = 0.052 \times 10^{-11}$m to $X_2 = 5.4 \times 10^{-11}$m and $\int_{0.052\times10^{-11}}^{5.4\times10^{-11}} (\sqrt{qEx - KE})dx = 11.9 \times 10^{-21}$. As a result, the tunneling probability is $T_{Na(i)} = 6.77 \times 10^{-28}$ (see Table 1).

Table 1. Comparison between intracellular and extracellular sodium ions in terms of concentration, kinetic energy, and tunneling probability.

Sodium Ion	Concentration (mEq/L)	KE (Joule)	Tunneling Probability
Intracellular	14	0.11×10^{-20}	6.77×10^{-28}
Extracellular	142	2.52×10^{-20}	1.16×10^{-19}

2.2.2. The Tunneling Probability of Potassium Ions

The diffusion potential (Nernst potential) of potassium ions is −94 mV [1]. So, the concentration difference of 136 mEq/L between intracellular potassium 140 mEq/L [1] and extracellular potassium 4 mEq/L [1] needs 94 mV to be balanced. Accordingly, the intracellular potassium concentration is balanced by 96.8 mV and the extracellular potassium concentration is balanced by 2.8 mV. In addition, the extracellular potassium ions will get additional kinetic energy due to the resting membrane potential (−90 mV). As a result, the intracellular potassium ions have kinetic energy equivalent to 96.8 mV and the extracellular potassium ions have kinetic energy equivalent to 92.8 mV.

Using Equation (4), the kinetic energy for intracellular potassium is $KE_{POTASSIUM(i)} = 1.55 \times 10^{-20}$J and the kinetic energy for extracellular potassium is $KE_{POTASSIUM(o)} = 1.48 \times 10^{-20}$J.

When tilt angle of alpha helix is 17° [17], $L = 4.4 \times 10^{-11}$m. Besides, the energy needed to open the gate of voltage-gated potassium channels (shaker type) is $14.19 Kcal/mole = 9.86 \times 10^{-20}$J [20] and consequently, $qE = 2.24 \times 10^{-9}$N.

Regarding the intracellular potassium ions, the forbidden region is from $X_1 = 0.7 \times 10^{-11}$m to $X_2 = 4.4 \times 10^{-11}$m and $\int_{0.7\times10^{-11}}^{4.4\times10^{-11}} (\sqrt{qEx - KE})dx = 7.2 \times 10^{-21}$, hence, the tunneling probability is $T_{K(i)} = 3.4 \times 10^{-22}$. On the other hand, the forbidden region for extracellular potassium is from $X_1 = 0.66 \times 10^{-11}$m to $X_2 = 4.4 \times 10^{-11}$m and $\int_{0.66\times10^{-11}}^{4.4\times10^{-11}} (\sqrt{qEx - KE})dx = 7.3 \times 10^{-21}$, therefore, the tunneling probability is $T_{K(o)} = 1.7 \times 10^{-22}$ (see Table 2).

Table 2. Between intracellular and extracellular potassium ions in terms of concentration, kinetic energy, and tunneling probability.

Potassium Ion	Concentration (mEq/L)	KE (Joule)	Tunneling Probability
Intracellular	140	1.55×10^{-20}	3.4×10^{-22}
Extracellular	4	1.48×10^{-20}	1.7×10^{-22}

Tunneling probability of the ions will differ according to the subtype of the voltage-gated channels because different channels have different values of barrier energy of the hydrophobic gate [20].

3. Quantum Conductance Due to Quantum Tunneling Current through the Closed Gate of the Channels

3.1. Quantum Conductance of Single Channel

Tunneling current through the gate of closed channels can be calculated using the following Equation [5]:

$$I = \frac{e^2 V}{4\pi^2 \hbar} T_{ion}, \quad (5)$$

where I is the tunneling current, e is the electron charge, V is the voltage across the channel, $\hbar$ is reduced Planck constant, and T_{ion} is the tunneling probability of the ion.

The aim is to calculate the conductance ($C = \frac{I}{V}$) and, by substituting the Equation (5) in the conductance equation, the quantum conductance due to quantum tunneling of ions through the closed channels is given by [5,21]

$$C = \frac{e^2}{4\pi^2\hbar} T_{ion}. \tag{6}$$

By applying this equation on sodium and potassium ions, single channel conductance due to quantum tunneling for these ions can be calculated (see Table 3).

Table 3. Single channel quantum conductance (C_{Qion}) of intracellular and extracellular ions.

Ion	Intracellular	Extracellular
Sodium	4.2×10^{-30} *	7.2×10^{-22} *
potassium	2.1×10^{-24} *	1.1×10^{-24} *

* the unit of the conductance in this table is milliSiemens (mS).

3.2. Quantum Membrane Conductance of Ions

The quantum membrane conductance per surface area unit is calculated by the following equation:

$$C_{QM} = C_{Qion} \times d, \tag{7}$$

where C_{QM} is the quantum membrane conductance per surface area unit, C_{Qion} is the single channel quantum conductance, and d is the density of voltage-gated channels in the membrane.

Voltage-gated potassium channels density in unmyelinated neurons is 5–50 channels/μm^2, while the density of voltage-gated sodium channels is 50–500 channels/μm^2 [22]. By taking the highest channel's density and substituting in Equation (7), the quantum membrane conductance of ions can be calculated (see Table 4).

Table 4. Quantum membrane conductance (C_{QM}) of intracellular and extracellular ions.

Ion	Intracellular	Extracellular
Sodium	2.1×10^{-19} *	3.6×10^{-11} *
Potassium	1.1×10^{-14} *	5.5×10^{-15} *

* the unit of conductance in this table is mS/cm^2.

3.3. The Effect of Quantum Conductance of Ions on the Resting Membrane Potential

At the resting state, there is membrane conductance of ions due to the leaky channels which determines the membrane potential when voltage-gated channels are closed [1]. The resting membrane conductance of potassium is 0.5 mS/cm^2 and that of sodium is 0.005 mS/cm^2 [1]. The quantum membrane conductance of ions should be substituted in the Goldman–Hodgkin–Katz equation to determine the effect of quantum tunnelling on the resting membrane potential as in the following equation [1]:

$$V(millivolts) = -61 \times \log \frac{[Na]_i(C_{Na} + C_{MQNa(i)}) + [K]_i(C_K + C_{MQK(i)})}{[Na]_o(C_{Na} + C_{MQNa(o)}) + [K]_o(C_K + C_{MQK(o)})}, \tag{8}$$

where V is the membrane potential, $[Na]_i$ is the intracellular sodium concentration, C_{Na} is the membrane conductance (due to leaky channels) of sodium, $C_{MQNa(i)}$ is the quantum membrane conductance of intracellular sodium, $[K]_i$ is the intracellular potassium concentration, C_K is the membrane conductance

(due to leaky channels) of potassium, $C_{MQK(i)}$ is the quantum membrane conductance of intracellular potassium, $[Na]_o$ is the extracellular sodium concentration, $C_{MQNa(o)}$ is the quantum membrane conductance of extracellular sodium, $[K]_o$ is the extracellular potassium concentration, and $C_{MQK(o)}$ is the quantum membrane conductance of extracellular potassium.

By substituting the values in Equation (8), there is no significant difference in the resting membrane potential before and after the substitution of quantum conductance of sodium and potassium ions because it is very small in comparison with the membrane conductance due to the leaky channels.

4. Discussion

The model of quantum tunneling of ions can be used to calculate the membrane conductance when the channels are closed. Additionally, it explains how closed channels could pass ions through even though no mechanical opening of the gate had occurred [23]. The results showed that the membrane conductance of ions due to quantum tunneling does not affect the resting membrane potential. However, under different circumstances such as change in the mass or charge of the passing ion and change in the amino acid residues of the hydrophobic gate, establishing a model for the quantum tunneling of ions through the closed channels will offer a useful tool to explain the biological phenomena that do not have a clear explanation and will provide a reasonable solution for any upcoming paradoxes, problems, or mysteries in the field of cell membrane biology, neuroscience, medicine, and many other fields. For example, the quantum conductance is inversely proportional to the mass of the ion, as a result, using lithium ions that are 3.3 times lighter than sodium will achieve significant exponential increase in their quantum conductance in comparison to that of extracellular sodium ions and, consequently, they will significantly affect the resting membrane potential of the neurons resulting in a therapeutic effect [7]. Moreover, this model helped in explaining the referred pain phenomenon by applying the Bernoulli trails equation on the tunneling probability [3]. Besides, this model is experimentally testable so the experiments can show the variations in ions' conductance according to the mass, the kinetic energy, and the energy barrier of the hydrophobic gate, and this will provide further evidence on the validity of the quantum tunneling of the ions in the biological systems.

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