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Magnesium Ions Depolarize the Neuronal Membrane via Quantum Tunneling through the Closed Channels

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Abstract: Magnesium ions have many cellular actions including the suppression of the excitability of neurons; however, the depolarization effect of magnesium ions seems to be contradictory. Thus several hypotheses have aimed to explain this effect. In this study, a quantum mechanical approach is used to explain the depolarization action of magnesium. The model of quantum tunneling of magnesium ions through the closed sodium voltage-gated channels was adopted to calculate the quantum conductance of magnesium ions, and a modified version of Goldman–Hodgkin–Katz equation was used to determine whether this quantum conductance was significant in affecting the resting membrane potential of neurons. Accordingly, it was found that extracellular magnesium ions can exhibit a depolarization effect on membrane potential, and the degree of this depolarization depends on the tunneling probability, the channels' selectivity to magnesium ions, the channels' density in the neuronal membrane, and the extracellular magnesium concentration. In addition, extracellular magnesium ions achieve a quantum conductance much higher than intracellular ones because they have a higher kinetic energy. This study aims to identify the mechanism of the depolarization action of magnesium because this may help in offering better therapeutic solutions for fetal neuroprotection and in stabilizing the mood of bipolar patients.

Keywords: quantum tunneling; quantum biology; resting membrane potential; magnesium; quantum conductance; depolarization

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1. Introduction

Magnesium has several uses in the medical field. It is used to treat eclampsia, asthmatic patients, and certain cardiac arrhythmias. Additionally, magnesium is a crucial cofactor for enzymes, and it is vital for ATP production [1]. Regarding its electrophysiological features, magnesium depolarizes the action potential threshold, decreases the frequency of action potentials, and consequently suppresses the overall activity and excitability of neurons. However, one contradictory feature of magnesium has been documented. This feature is the ability of magnesium ions to depolarize resting membrane potential, which increases the excitability of neurons in contrast to the actual actions of magnesium, but the overall net effect is to suppress excitability [2,3].

Several hypotheses have been proposed to explain the depolarization effect of magnesium ions, including the inhibition of the activity of certain types of potassium channels that favor a depolarized membrane and the increase of the activity of the 1 Na^+ /1 Mg^{2+} antiport that depolarizes membranes [2,3]. However, in the present study, a quantum mechanical approach is used to explain the depolarization effect of magnesium ions.

A model of quantum tunneling of ions through closed channels has been postulated [4] and used to explain and understand different phenomena and actions that occur in biological systems such as referred pain [5], the action of lithium to stabilize the mood of bipolar patients [6], and myelin function in spatiotemporally confining action potentials and limiting hyperexcitability [7]. Therefore, this model is used in this study to explore how magnesium ions could depolarize the neuronal membrane.

Moreover, the depolarization effect of magnesium ions might be responsible for their fetal neuroprotection action [8–10] and for a mood stabilizing action similar to lithium in treating bipolar patients [11], because it has been found that depolarization of the neuronal membrane activates DNA synthesis and mitosis in arrested neurons that exhibit neuroprotection actions [12–16]. Additionally, it has been postulated that lithium stabilizes the mood of bipolar patients by depolarizing the hyperpolarized membrane of their cells [6]. Thus, identifying the exact mechanism behind the depolarization effect of magnesium may offer better therapeutic solutions to treat several disorders and diseases.

2. Methods

The proposed mechanism is that magnesium ions tunnel through the closed channels of the neuronal membrane. The closed voltage-gated channels block the permeation of ions by forming a hydrophobic gate at the intracellular end of the membrane [17]. Therefore, the quantum tunneling phenomenon is applied on this gate [4]. The hydrophobic gate has been illustrated as an electric field in the space of parallel capacitor that resists ion movement [4]. This illustration is done to better determine how the barrier energy of the gate changes with ion's position while passing through the closed gate. The model of quantum tunneling is applied on the sodium voltage-gated channel Nav1.2.

The tunneling probability of magnesium ions through the closed sodium voltage-gated channels can be calculated by the following equation [4,18]:

$$T_Q = e^{-\frac{\sqrt{8m}}{\hbar}\int_{X1}^{X2}\sqrt{(qEx)_{gate}-E_K}dx} \tag{1}$$

where T_Q is the tunneling probability, m is the mass of magnesium ion (4.04×10^{-26} Kg), $\hbar$ is the reduced Planck constant (1.05×10^{-34} Js), q is the charge of magnesium ion(3.2×10^{-19} C), E_{gate} is the electric field required to prevent the ion from passing the gate, x is the position of the ion through the gate, E_K is the kinetic energy of magnesium ion, and X_1–X_2 is the forbidden region where magnesium ions cannot pass the gate.

The electric field E_{gate} is calculated by the following equation [4]:

$$E_{gate} = \frac{U}{qL} \tag{2}$$

where U is the energy that is needed to open the closed gate of the channels, q is the charge of magnesium ion, and L is the length of the sodium channel gate 5.4×10^{-11} m [4].

To calculate U, the following equation can be used [19]:

$$U = q_{gate}eV_{1/2} \tag{3}$$

where q_{gate} is the gating charge, e is the electron charge (-1.6×10^{-19} C), and $V_{1/2}$ is the membrane voltage at which half of channels are open.

On the other hand, when extracellular magnesium ions pass through the channels and reach the intracellular hydrophobic gate, they get kinetic energy from the neuronal membrane voltage of −90 mV [20]. In addition, they get kinetic energy from the thermal source of the body temperature; hence, their total kinetic energy can be calculated by the following equation:

$$E_{K(o)} = qV_m + \frac{1}{2}K_BT \tag{4}$$

where q is the magnesium ion charge, V_m is the neuronal membrane voltage of −90 mV [20], K_B is the Boltzmann constant (1.38×10^{-23} J/K), and T is the absolute body temperature 310 K.

Regarding intracellular magnesium ions, the neuronal membrane voltage does not contribute to their kinetic energy because the gate is located at the intracellular end so that intracellular magnesium ions hit the gate before going through the membrane voltage. Therefore, their kinetic energy is due to the thermal source of the body temperature, and it can be calculated by the following equation:

$$E_{K(i)} = \frac{1}{2} K_B T \tag{5}$$

The forbidden region X_1–X_2 is where the barrier energy is equal or higher than the kinetic energy of magnesium ion: $qEx \geq E_K$.

To investigate the effect of the quantum tunneling of magnesium ions on resting membrane potential, the quantum conductance of single channel and the quantum membrane conductance of magnesium ion must be calculated.

The quantum conductance of single channel for magnesium ion C_{QMg} can be calculated by the following equation [4,18,21]:

$$C_{QMg} = \frac{q^2}{h} T_Q \left(\frac{P_{Mg}}{P_{Na}}\right) \tag{6}$$

where q is the charge of magnesium ion, h is the Planck constant ($6.6 \times 10^{-34}\ J_S$), T_Q is the tunneling probability, and $(\frac{P_{Mg}}{P_{Na}})$ represents the degree of sodium channels' selectivity to magnesium ions in comparison to sodium ions.

Additionally, the quantum membrane conductance can be calculated by the following equation:

$$C_{QM(Mg)} = C_{QMg} \times D \tag{7}$$

where D is the density of sodium channels in the neuronal membrane.

Magnesium ions are divalent ions. Therefore, to determine the effect of magnesium ions on the resting membrane potential, the Goldman–Hodgkin–Katz equation of monovalent ions must be modified as in the following [22]:

At equilibrium, the net ions movement across the neuronal membrane is zero:

$$0 = J_{Na^+} + J_{K^+} + J_{Mg^{+2}} \tag{8}$$

where J is the current density (A/m^2).

$$0 = Y_{Na} \frac{(w[Na]_i - [Na]_o)}{w-1} + Y_K \frac{(w[K]_i - [K]_o)}{w-1} + Y_{Mg} \frac{(w^2[Mg]_i - [Mg]_o)}{w^2-1}$$

where $Y_{ion} = P_{ion} z^2 V_m \frac{F^2}{RT}$ and $w = e^{\frac{FV_m}{RT}}$, where P_{ion} is the membrane permeability to the ion (m/s), z is the valence of the ion, V_m is the membrane potential, F is the Faraday constant, R is the gas constant, and T is body temperature. Y_{ion} values can be replaced by any proportional values that satisfy Equation (8). Therefore, they are replaced by the values of membrane conductance of ions C_{ion} (mS/cm^2). Taking into consideration the quantum conductance of magnesium ions and that conductance is not the same for extracellular and intracellular magnesium, as is shown further in the discussion, the equation becomes:

$$0 = \frac{C_{Na}(w[Na]_i - [Na]_o)}{w-1} + \frac{C_K(w[K]_i - [K]_o)}{w-1} + \frac{(C_{QM(Mg)i} w^2 [Mg]_i - C_{QM(Mg)o}[Mg]_o)}{w^2-1}$$

By removing the factor $(w - 1)$ and multiplying by $(w + 1)$, the equation becomes:

$$0 = (w+1)C_{Na}(w[Na]_i - [Na]_o) + (w+1)C_K(w[K]_i - [K]_o) + (C_{QM(Mg)i} w^2 [Mg]_i - C_{QM(Mg)o}[Mg]_o)$$

By ordering and extending:

$$w^2(S_2 + M_2) + w(S_2 - S_1) = S_1 + M_1 \tag{9}$$

where:

$$S_1 = C_{Na}[Na]_o + C_K[K]_o \tag{10}$$

$$S_2 = C_{Na}[Na]_i + C_K[K]_i \tag{11}$$

$$M_1 = C_{QM(Mg)o}[Mg]_o \tag{12}$$

$$M_2 = C_{QM(Mg)i}[Mg]_i \tag{13}$$

Equation (9) is a simple quadratic equation that can be solved after some rearranging:
$w^2 + Aw = B$ where $A = \frac{S_2 - S_1}{S_2 + M_2}$ and $B = \frac{S_1 + M_1}{S_2 + M_2}$
Completing the square:

$$\left(w + \frac{A}{2}\right)^2 - \frac{A^2}{4} = B$$
$$w = -\frac{A}{2} \pm \sqrt{B + \frac{A^2}{4}}$$

The positive value of (w) is chosen because the negative value is not compatible with exponential function. Therefore:

$$w = -\frac{A}{2} + \sqrt{B + \frac{A^2}{4}}$$
$$w = \frac{S_1 - S_2}{2(S_2 + M_2)} + \sqrt{\frac{S_1 + M_1}{S_2 + M_2} + \frac{(S_2 - S_1)^2}{4(S_2 + M_2)^2}}$$
$$w = \frac{S_1 - S_2}{2(S_2 + M_2)} + \sqrt{\frac{4(S_1 + M_1)(S_2 + M_2) + (S_2 - S_1)^2}{4(S_2 + M_2)^2}}$$
$$w = \frac{1}{2(S_2 + M_2)}\left[(S_1 - S_2) + \sqrt{4S_1S_2 + 4S_1M_2 + 4S_2M_1 + 4M_1M_2 + S^2{}_1 - 2S_1S_2 + S_2{}^2}\right]$$

Finally, (w) can be represented by the following equation:

$$w = \frac{1}{2(S_2 + M_2)}\left[(S_1 - S_2) + \sqrt{(S_1 + S_2)^2 + 4(S_1M_2 + S_2M_1 + M_1M_2)}\right] \tag{14}$$

3. Results and Discussion

The sodium channel Nav1.2, with the gating charge $q_{gate} = 9.2$ [23] and $V_{1/2} = -43$ mV [24], requires $U = 6.33 \times 10^{-20}$ J to open its closed hydrophobic gate. Therefore, by using Equation (2), $E_{gate} = 3.66 \times 10^9$ V/m. Additionally, by using Equations (4) and (5), the kinetic energy of extracellular magnesium ions $E_{K(o)} = 3.09 \times 10^{-20}$ J, while the kinetic energy of intracellular magnesium ions $E_{K(i)} = 0.21 \times 10^{-20}$ J. As a result, the forbidden region for extracellular magnesium ions is from $X_1 = 2.64 \times 10^{-11}$ m to $X_2 = 5.4 \times 10^{-11}$ m, and the forbidden region for intracellular magnesium ions is from $X_1 = 0.18 \times 10^{-11}$ m to $X_2 = 5.4 \times 10^{-11}$ m.

Accordingly, by using Equations (1), (6) and (7), the tunneling probability, quantum conductance of single channel C_{QMg}, and the quantum membrane conductance $C_{QM(Mg)}$ can be calculated. See Table 1.

Table 1. Charge, mass, kinetic energy, quantum tunneling probability, quantum conductance of single channel C_{QMg}, and the quantum membrane conductance $C_{QM(Mg)}$ for extracellular and intracellular magnesium ions.

Magnesium Ion	Charge (C)	Mass (Kg)	Kinetic Energy (J)	Tunneling Probability	C_{QMg} [1] (mS)	$C_{QMg(Mg)}$ [2] (mS/cm^2)
Extracellular	3.2×10^{-19}	4.04×10^{-26}	3.09×10^{-20}	1.54×10^{-8}	2.39×10^{-10}	1.2
Intracellular	3.2×10^{-19}	4.04×10^{-26}	0.21×10^{-20}	5.13×10^{-21}	7.96×10^{-23}	3.98×10^{-13}

[1] (P_{Mg}/P_{Na}) is substituted to be 0.1 [25]; [2] the channels density (D) is substituted to be 50 channels/μm^2 [26].

By substituting 142 mmol/L, 14 mmol/L, 4 mmol/L, 140 mmol/L [20], 0.48 mmol/L (free magnesium "unbound") [27], 0.005 mS/cm^2, 0.5 mS/cm^2 [20], and 1.2 mS/cm^2 for the following variables $[Na]_o$, $[Na]_i$, $[K]_o$, $[K]_i$, $[Mg]_o$, C_{Na}, C_K, and $C_{QM(Mg)o}$, respectively, in Equations (10)–(12), S_1 = 2.71, S_2 = 70.07, and M_1 = 0.58. M_2 are considered to be zero because the quantum membrane conductance of intracellular magnesium ions is very small in comparison to other values in a way that does not affect results.

Then, by substituting the values of S_1, S_2, M_1 and M_2 into Equation (14), $w = 4.66 \times 10^{-2}$.

Finally, by substituting the value of (w) in this equation $w = e^{\frac{FV_m}{RT}}$, the resting membrane potential (V_m) becomes −82 mV after being −86 mV in the absence of magnesium ions. This shows the depolarization effect of magnesium ions under physiological concentrations because the membrane potential becomes less negative by around 4 mV. However, if (P_{Mg}/P_{Na}) is assumed to be 0.01, the depolarization is less significant because, in this case, the quantum conductance is lower. However, if the above calculations are repeated, but this time with P_{Mg}/P_{Na} = 0.01 [25] and an extracellular free magnesium concentration $[Mg]_o$ = 5.5 mmol/L, as in the experimental studies [2], the resting membrane potential becomes −81 mV with membrane depolarization by around 5 mV. Furthermore, the quantum conductance of extracellular magnesium ions is higher than that for intracellular magnesium ions because they have higher kinetic energy, and that means a higher tunneling probability and, consequently, a higher quantum conductance.

Note that the neuronal resting membrane potential is −90 mV, in which potassium and sodium conductance contributes by −86 mV and the sodium–potassium pump contributes by −4 mV [20].

Therefore, there are several factors that determine the degree of depolarization by magnesium ions including the tunneling probability, the sodium channels' selectivity to magnesium ions, the sodium channels' density in the neuronal membrane, and the magnesium ions' concentration.

The membrane conductance of sodium ions of 0.005 mS/cm^2 is due to leaky channels [20] not the closed voltage gated channels. To compare the sodium and magnesium ions in terms of quantum conductance, see Table 2.

Table 2. The charge, mass, kinetic energy, quantum tunneling probability, quantum conductance of single channel C_{QNa}, and quantum membrane conductance $C_{QM(Na)}$ for extracellular and intracellular sodium ions.

Sodium Ion	Charge (C)	Mass (Kg)	Kinetic Energy (J)	Tunneling Probability	C_{QNa} [1] (mS)	$C_{QM(Na)}$ [2] (mS/cm^2)
Extracellular	1.6×10^{-19}	3.8×10^{-26}	1.65×10^{-20}	7.36×10^{-14}	2.85×10^{-15}	1.43×10^{-5}
Intracellular	1.6×10^{-19}	3.8×10^{-26}	0.21×10^{-20}	2.34×10^{-20}	9.1×10^{-22}	4.55×10^{-12}

[1] $C_{QNa} = \frac{e^2 T_Q}{h}$, [2] the channels density (D) is substituted to be 50 channels/μm^2 [26].

It is clear that the quantum conductance of extracellular magnesium is much higher than the quantum conductance of extracellular sodium because the charge of magnesium ions is two times higher than that of sodium (magnesium ion is a divalent ion, while sodium ion is a monovalent ion), which leads to higher kinetic energy while passing through the membrane voltage and, thus, a higher tunneling probability and a higher quantum conductance. Regarding the quantum conductance of intracellular ions, there is a small difference between the two ions, and this difference can be attributed to the small difference in their masses.

4. Conclusions

Extracellular magnesium ions can exhibit a depolarization effect on membrane potential because they can achieve a significant quantum membrane conductance. This quantum conductance is higher than the quantum conductance of intracellular magnesium ions because extracellular magnesium ions a have higher kinetic energy. In addition, the quantum membrane conductance of extracellular magnesium is higher than that of extracellular sodium because magnesium ions are divalent ions, which means that they get a higher kinetic energy while passing through the neuronal membrane voltage.

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