A Theoretical Study to Explain the Referred Pain Phenomenon and Its Characteristics via Quantum Tunneling of Potassium Ions Through the Channels of Neuronal Membrane

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ABSTRACT

When action potentials occur in neurons, sodium ions diffuse to inside neuronal membrane during depolarization whereas potassium ions diffuse to the outside during repolarization, in which an increase in extracellular potassium concentration occurs each and every single time a neuron fires. This escalation in potassium concentration will surround neighboring neurons. Hence, I calculated that minute increase in potassium concentration. These potassium ions will hit the closed channels in the membrane of neighboring unstimulated neurons, however, they will not be able to pass since their kinetic energy is less than the energy needed to open the closed channels. Given these points, I calculated the probability of potassium ions to tunnel through closed channels. Moreover, I calculated the membrane conductance made by the potassium tunneling and the threshold of potassium conductance needed to stimulate neighboring neurons, only to find that the actual conductance was less than the theorized threshold. For that reason, I calculated the potassium ions' probability to reach the proposed threshold, while also using Bernoulli trials equation to calculate the probability of action potential induction. Accordingly, I used the potassium tunneling model to explain the referred pain phenomenon and its characteristics, moreover, filling the gaps in referred pain theories which could not explain all of its characteristics.

Key Words: quantum tunneling, referred pain, unmyelinated C-fiber, visceral pain, potassium channel

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Introduction

Referred pain is the pain that occurs at distant site away from the local site where the pathology or the disease originates, and it is often associated with visceral pain that is transmitted via the small unmyelinated C-fibers. There are many examples on referred pain such as: the pain referred from myocardial infarction (heart attack) to the shoulder and arm, the pain referred from the appendix to the umbilicus and many other examples(Hall, 2015). Referred pain is important in the clinical practice since many patients come only with a pain which is away from the original site of disease (Hall, 2015). There are several theories that aimed to explain the referred pain, however, each theory has defects and limitations of giving a comprehensive mechanism of referred pain (Arendt-Nielsen and Svensson, 2001).

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For instance, convergence projection theory is not able to explain the time delay in the appearance of referred pain and is not compatible with that local and referred pain have different thresholds as well as it does not explain why referred pain is distally unidirectional phenomenon (Arendt-Nielsen and Svensson, 2001). Also, the hyperexcitability theory does not explain why there is more time delay in animal models in comparison with humans in which animal models need minutes for referred pain to occur, whereas humans need seconds. Moreover, it is in conflict with the majority of the experimental studies as referred pain spreads distally and rarely proximally (Arendt-Nielsen and Svensson, 2001). Additionally, axon reflex theory and convergence facilitation theory lack some of referred pain characteristics (Arendt-Nielsen and Svensson, 2001). Therefore, the gaps in these theories could be conceptualized in a comprehensive fashion through the utilization of quantum mechanics.

One of the major consequences of quantum mechanics is quantum tunneling which is a quantum phenomenon in which small particles are able to go through a barrier even though that their kinetic energy is less than the energy needed to pass that barrier. These small particles have the behavior of waves that enables them to get a non-zero probability to tunnel an energy barrier. Additionally, this probability depends on the length of the barrier and its energy and the particle kinetic energy (Serway, 1990).

Thus, the aim of this theoretical study is to fill the gaps in the referred pain theories and explain its characteristics using the potassium ion tunneling model. Filling the gaps might give a comprehensive theory for referred pain and set the foundation that quantum mechanics plays an important role in the biological systems of neurons. Moreover, this might help in explaining the idiopathic and unknown origins of many diseases specifically in the clinical neurology.

Mathematical Modeling of Potassium Tunneling

Change in potassium concentration during action potential

The transmission of each action potential along a nerve fiber reduces slightly the concentration difference of potassium inside and outside the membrane because potassium ions diffuse to the outside during repolarization (Hall, 2015), thus I calculate the slight increase in extracellular potassium concentration during action potential $[K^+]_{AP}$ using the following equation:

$$\left[K^+\right]_{AP} = \frac{N}{N_A V_{ol}} \quad (1)$$

where Vol is the volume between stimulated neuron of the local area and the neuron of the referred area where potassium ions diffuse and this volume takes approximately the shape of cylinder in which the center is the local neuron and the boundary is the collection of neighboring neurons (see fig. 3), N is the number of potassium ions exit from the neuron per action potential per surface area unit and N_A is Avogadro's number (Fig. 1).

To calculate $[K^+]_{AP}$, the following steps should be considered:

1. I have to calculate N :

(a) During the action potential, the average potassium ion conductance C is calculated as:

$$C = \frac{C_H + C_L}{2} \quad (2)$$

Where C_H is the highest potassium conductance during repolarization phase of action potential and C_L is the lowest potassium conductance.

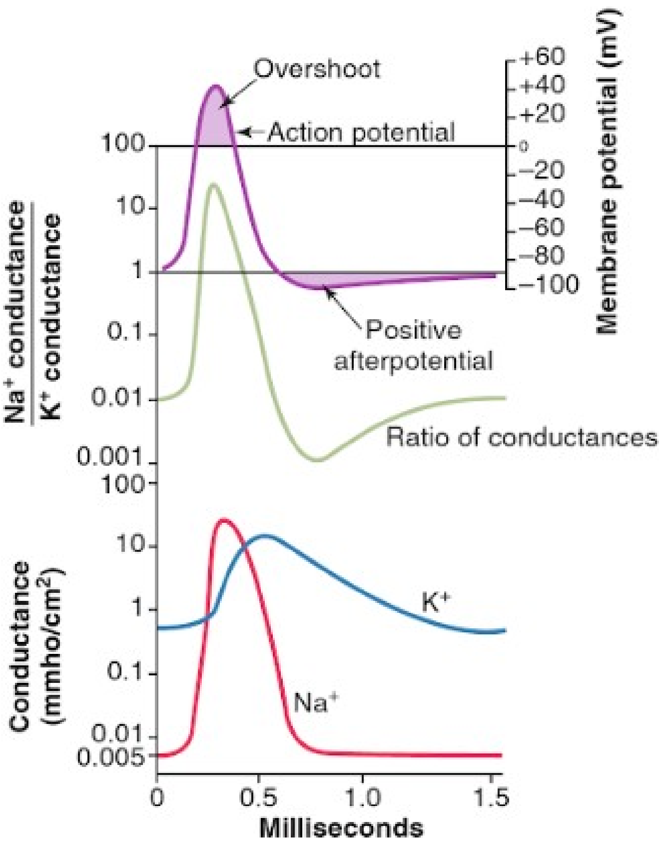

Figure 1. Changes in potassium conductance (indicated by blue curve) and membrane potential (indicated by purple curve) during an action potential (Hall, 2015).

Potassium conductance is between C_H = 10 *mmho/cm*^{2} and C_L = 0.5 *mmho/cm*^{2} (Hall 2015)(see fig.1) and consequently, the average potassium conductance is C = 5.25 *mmho/cm*^{2}.

(b) I calculate the average voltage (driving force) of potassium V during repolarization phase by the following equation:

$$V = \frac{(V_i - V_{K+}) + (V_E - V_{K+})}{2} \quad (3)$$

Where V_i is the membrane potential at the beginning of repolarization and it is +35 mV, V_E is the membrane potential at the end of repolarization and it is -90 mV and V_{K+} is the diffusion potential of potassium ion and it is -94 mV (Hall 2015).I calculate the average voltage of potassium and it is 66.5 mV.

(c) then I calculate the current density by:

$$C = \frac{I}{V} \quad (4)$$

where C is the electric conductance, I is the current density and V is the voltage.

By substituting the average conductance and the average voltage of potassium during repolarization phase, which are calculated in step (a) and (b), in the equation (4), I = 3.49 *amp/m*^{2}.

(d) Eventually, N can be calculated using this equation:

$$I = \frac{Ne}{t} \quad (5)$$

where I is the current density, N is the number of potassium ions exit from the neuron per action potential per surface area unit,e is the electron charge and t is time of repolarization phase of action potential. By substituting current density I and time t, which is approximately 0.2 mS (Hall 2015), then N = 4.36 × 10^{15} K^+*ions/m*^{2} =1.37 × 10^6 K^+*ions/*314 *μm*^{2}.

2. the volume, in which potassium ions diffuse as in fig. 3, can be calculated by:

$$Vol = \pi r_l^2 L \quad (6)$$

where Vol is the volume, r_l is the linear distance between neureons and it is on average 30 *μm* (Waser 2012) and L is the length of a part of neuron (see fig.2).

I assume that L = 100 *μm* to get surface area of neuron membrane A = 314 *μm*^{2} as in this equation:

$$A = 2\pi r_N L \quad (7)$$

where A is the surface area and r_N is the radius of unmyelinated C- fiber and it is on average 0.5*μm* (Purves *et al.*, 2004).

By substituting in equation (6), Vol = 2.83 × 10^{-13}*m*^{3}.

3. and finally V and N can be substituted in equation (1) to get $[K^+]_{AP}$ = 8.04×10^{-6} mmole/L.

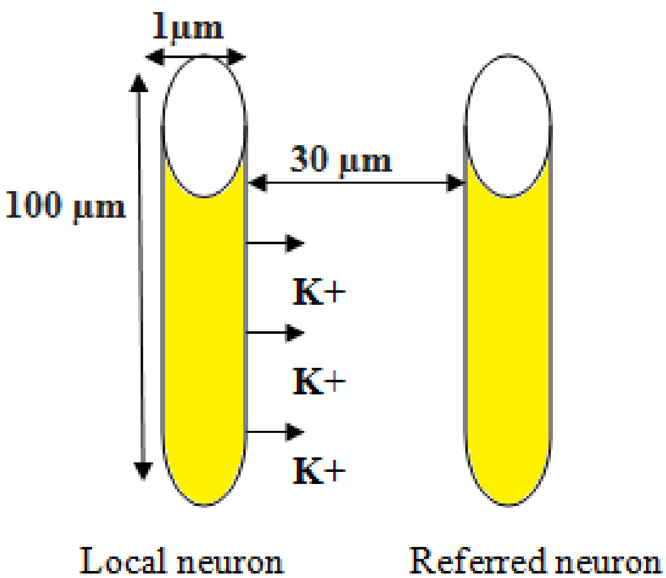

Figure 2. Represents the distance between local and referred neurons 30 *μm*, a length of a part of neuron 100 *μm* and diameter of 1 *μm* with 314 *μm*^{2} surface area through which 1.37 × 10^6 potassium ions diffuse into extracellular fluid for each action potential.

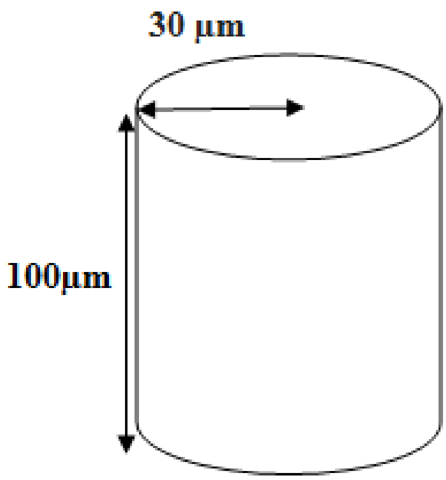

Figure 3. The volume in which potassium ions diffuse during action potential. It takes the shape of cylinder where the length is the same as the length of the part of a neuron and the radius is the same as the distance between the neurons (see fig. 2).

Tunneling probability of potassium ions through closed channels.

Voltage-dependent potassium channels (shaker type for example) are composed out of four alpha-subunits, each having six membrane-spanning alpha-helices (S1-S6). In addition, K+ permeation through the pore of the channel can be sealed off mainly by the inner S6 bundle crossing (BC gate) by forming a hydrophobic constriction (see fig.4). Furthermore, the BC gate of shaker type is comprised of one or two hydrophobic residues responsible for the sealing off K+ passage through the closed channel (Labro and Snyders, 2012). In addition to that, the average kink angle of the S6 helices corresponding to the closed state (see fig.5) is 17°-14° (Fowler and Sansom, 2013). For that reason, Potassium ions coming from the extracellular fluid during action potential will pass the selective filter of the closed channels of referred neurons, however, they will not pass the closed BC gate, as a result they will not pass the channels but they will go through most of the voltage difference of neuronal membrane of 90 mV sparing the small voltage difference across the BC gate (Hall, 2015). Neglecting the effect of potassium ions extracellular concentration on their kinetic energy because it is minimal in comparison to the effect of voltage difference and by neglecting the value of the small voltage difference across the gate on the 90 mV (Hall, 2015), I calculate the potassium ions kinetic energy when they reach the gate using the following equation:

$KE = V\,e$ (8)

where KE is kinetic energy, V is voltage difference across neuron membrane (90 mV) and e is charge of electron, and by substituting in the equation, KE = 1.44×10^{-20} J but the energy that the potassium ions should have to pass through the closed channel (shaker type) is 14.19 kcal/mole = 9.86×10^{-20} J per one channel (Islas, 2016) and this energy represents the energy of the barrier U , so it is obvious that KE is less than U and tunneling probability can be calculated.

Alpha-helix of S6 segment has a helical structure which is composed of turns and each turn has around 3.6 residues (Lodish *et al.*, 2008) with a length of 5.4×10^{-10} m which means 1.5×10^{-10} m for each residue (Moran *et al.*, 2014) (see fig.6 and 7). With tilt angle of 17 (Fowler and Sansom, 2013) the vertical length L, which represents the length of energy barrier that potassium ions can tunnel through (see fig.5), is calculated as:

$L = R \sin\theta$ (9)

Where R is the length of one residue and θ is the tilt angle, then the vertical length L = 4.4×10^{-11} m.

Assuming that BC gate is sealed off by one hydrophobic residue (Labro and Snyders, 2012), then

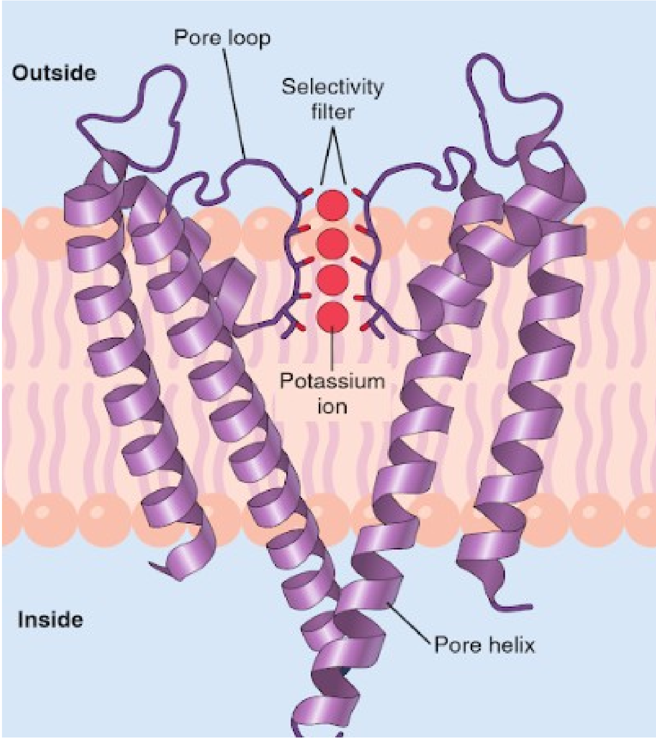

Figure 4. The structure of a potassium channel which has a selective filter and a point of S6 bundle crossing at the intracellular side (Hall, 2015).

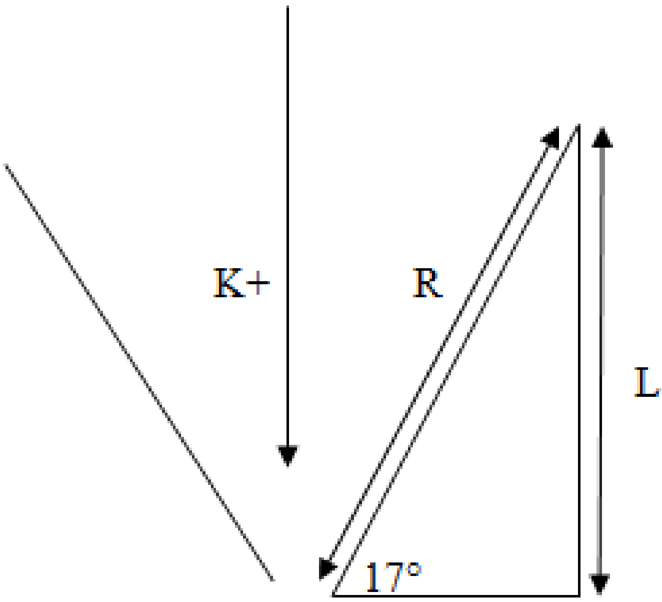

Figure 5. Represents the vertical length L of energy barrier that potassium ion will tunnel and the tilt angle of 17°.

it will represent the energy barrier for potassium ion passage. Additionly, I divide this barrier into 6 parts and in each part $L=4.4 \times 10^{-11}/6 = 7.33 \times 10^{-12}$ m and $U = 9.86\times10^{-20}/6 = 1.64 \times 10^{-20}$ J ensuring that U for each part is still higher than KE of potassium ions. Accordingly, I calculate the tunneling probability in each part of the barrier using the following equation:

$T_p = exp(-2LK)$ (10)

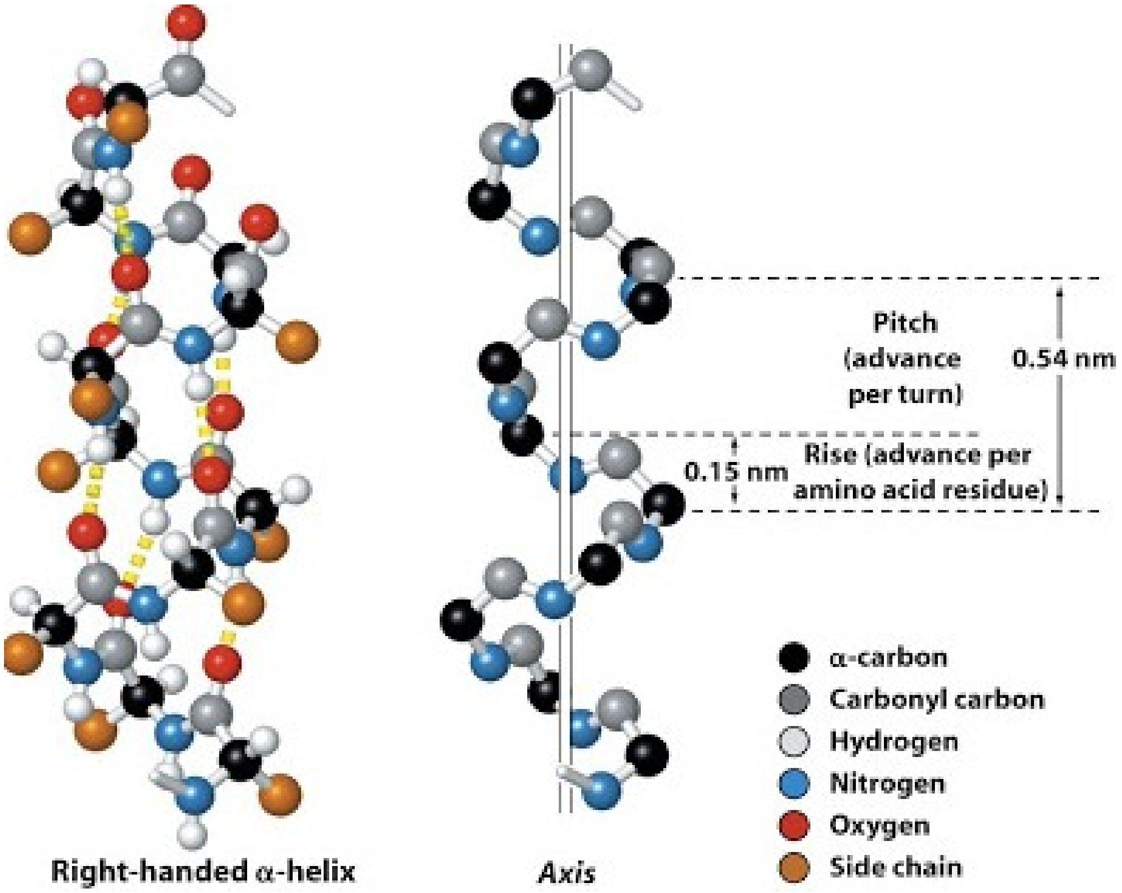

Figure 6. The length of the turn in alpha-helix (Moran et al., 2014).

Where L is the length of each part of the barrier, and K is given by:

$$K = \frac{\sqrt{2m(U - KE)}}{\hbar} \quad (11)$$

where m is the mass of potassium ion and ħ is reduced planck constant.

By substituting the values in equation (11) and equation (10), T_p = 0.106, and since potassium ion must tunnel each part of the barrier, then the total probability to pass through the entire barrier is $T_t = (0.106)^6 = 1.42 \times 10^{-6}$. Besides, potassium channel density in unmyelinated axons is 5 – 50 *channels/μm²* (Caldwell 2009) with average 28 channels/μm^2 and pore radius of potassium channel is $r = 4.5 \times 10^{-10}$m (Moldenhauer *et al*. 2016) with surface area of the pore $A = 6.36 \times 10^{-19} m^2$ and that means a potassium ion does not always hit the channel because not all of the neuronal membrane surface area is embedded by potassium channels. For that reason, the probability of potassium ion to hit a channel at a given area in the membrane is $T_h = 6.36 \times 10^{-19} \times 28/10^{-12} = 1.78 \times 10^{-5}$. As a result, the overall probability for a potassium ion to hit and tunnel a channel is $T_C = 1.42 \times 10^{-6} \times 1.78 \times 10^{-5} = 2.53 \times 10^{-11}$.

Calculating the potassium conductance due to quantum tunneling (or Quantum potassium conductance), the threshold of conductane and the probability to induce action potential

The current density due to quantum tunneling is given by the following equation (Serway et al., 1990):

$$I = \frac{e^2 VK}{4\pi^2 L\hbar} Tc \quad (12)$$

where e is electron charge, V is the voltage difference across the barrier, K is given in equation (11), L is the length of energy barrier, ħ is reduced planck constant and T_C is the total probability for channel hitting and tunneling.

By substituting equation (12) in equation (4), the quantum conductance of potassium ion *CQK* can be calculated as:

$$C_{QK} = \frac{e^2 K}{4\pi^2 L\hbar} Tc \quad (13)$$

C_{QK} in equation (13) represents the potassium conductance due to quantum tunneling through the entire barrier, hence I substitute $U = 9.86 \times 10^{-20} J$, $KE = 1.44 \times 10^{-20} J$, $L = 4.4 \times 10^{-11} m$ and $T_C = 2.53 \times 10^{-11}$ to get $C_{QK} = 3.5 \times 10^9 mmho/m^2$.

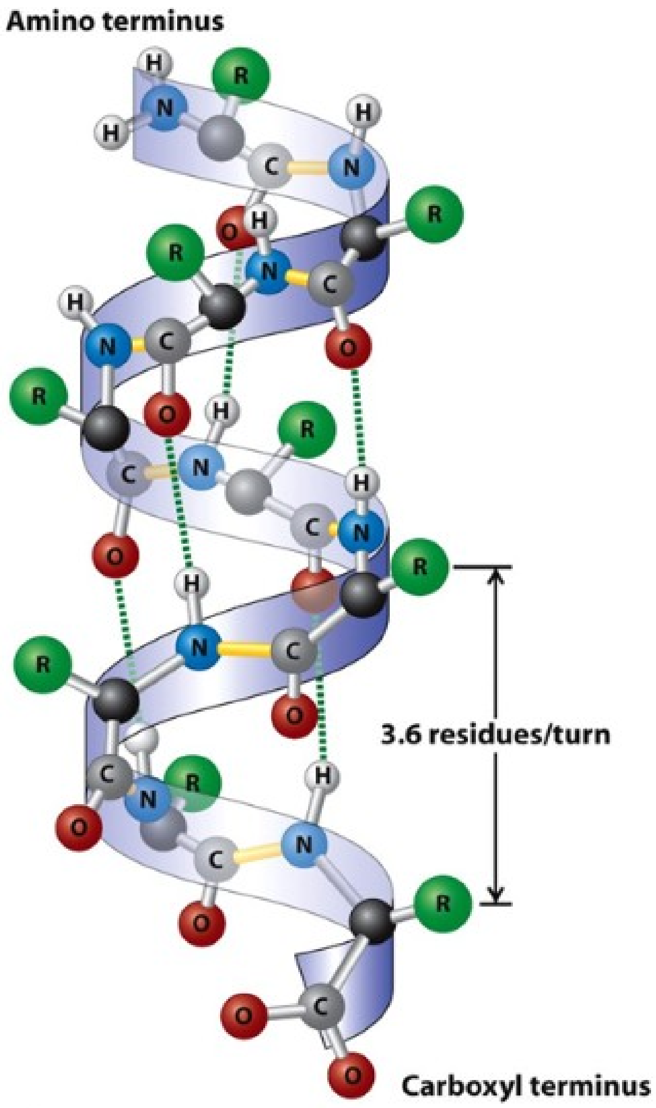

Figure 7. The structure of alpha-helix with 3.6 residues for each turn (Lodish et al., 2008).

But with pore radius of potassium channel r = 4.5×10^{-10} m (Moldenhauer *et al.*, 2016), the surface area of the pore A = $6.36 \times 10^{-19} m^2$ and consequently the conductance of a single potassium channel is calculated as:

$C_{potassium-channel} = C_{QK} A$ (14)

then $C_{potassium-channel} = 2.23 \times 10^{-9} mmho$.

Potassium channel density in unmyelinated axons is 5 – 50 *channels/μm*² (Caldwell, 2009) which means that the quantum potassium conductance by its maximum value through a neuron membrane $CQKM$ is $50 \times 2.23 \times 10^{-9} = 11.2 mmho/cm^2$.

The membrane potential of the neuron should reach -65 mV above the resting membrane potential of-90 mV to induce action potential (Hall, 2015), hence I calculate the threshold of quantum potassium conductane of neuron membrane C_{QKMT} to induce action potential using Goldman equation of membrane potential (Hall, 2015):

$$V_m(millivolts) = -61 \times \log \frac{[Na^+]_i C_{Na^+} + [K^+]_i C_{K^+}}{[Na^+]_o C_{Na^+} + [K^+]_o C_{K^+} + [K^+]_{AP} C_{QKMT}} \quad (15)$$

where $[K^+]_{AP}$ is the increase in extracellular potassium concentration calculated in section 2.1, $[Na^+]_i$ is intracellular sodium concentration and it is 14 mmole/L, $CNa+$ is sodium ion conductance through the membrane at resting state and it is $0.005 mmho/cm^2$ (see fig.1), $[K^+]_i$ is intracellular potassium concentration and it is 140 mmole/L, C_{K+} is potassium ion conductance through the membrane at resting state and it is $0.5 mmho/cm^2$ (see fig.1), $[Na^+]_o$ is extracellular sodium concentration and it is 142 mmole/L and $[K^+]_o$ is extracellular potassium concentration and it is 4 mmole/L (Hall, 2015).

By substituting in equation (15), $C_{QKMT} = 4.04 \times 10^5\ mmho/cm^2$.

It is clear that quantum potassium conductance of neuron membrane C_{QKM} is less than threshold of conductance to induce action potential C_{QKMT}, therefore I calculate the threshold of tunneling probability through the closed channel $T_{T\,C}$ to achieve the threshold of conductance as in the following steps:

1. Assuming that at least one channel is needed to be tunneled in a surface area of $1 \mu m^2$ of neuron membrane to induce action potential, as a result the conductance of a single potassium channel should be $C_{potassium-channel} = C_{QKMT} \times 1\ \mu m^2 = 4.04 \times 10^{-6} mho$.
2. Then I calculate the conductane per surface area unit of potassium channel pore C_{QK} =

$C_{potassium-channel} / A_{pore} = 4.04 \times 10^{-6} mho / 6.36 \times 10^{-19} m^2 = 6.35 \times 10^{12} mho/m^2$.

3. By substituting in equation (13), I calculate $T_{TC} = 4.57 \times 10^{-5}$. T_{TC} also represents the minimum fraction of potassium ions that should tunnel to induce action potential and any fraction equals or higher than 4.57×10^{-5}, it will induce action potential.

Using Bernoulli trials equation to calculate the probability to induce action potential through the surface area of referred neuron membrane available for tunneling.

In this section, I use Bernoulli trial equation which is a mathematical expression used to calculate the probability of making successful trials when independent repeated trials are made:

$$P(Z) = \frac{N!P^z(1-P)^{N-Z}}{(N-Z)!Z!} \quad (16)$$

Where N is the number of total trials,P is the probability of success, Z is the number of successful trials that I want to calculate the probability to achieve P (Z). If $Z = 0$, then $P(0) = (1 - P)^N$.

As in section 2.1, the number of potassium ions per surface area diffusing into extracellular fluid is $4.36 \times 10^3/\mu m^2$ and the average density of potassium channels is 28 channels/ μm^2, therefore, on average there are 1.56×10^2 potassium ions trying to hit a channel. If at least one of these potassium ions will hit and tunnel the channel, the tunneling fraction will be $1/1.56 \times 10^2 = 6.4 \times 10^{-3}$ which is higher than 4.57×10^{-5} and consequently an action potential will be induced.

Using Bernoulli trials, I calculate the probability that at least one of the potassium ions will hit and tunnel through the channel as the following:

$P_a = 1 - P(0)$

$= 1 - (1 - T_C)^{156}$

$= 1 - (1 - 2.53 \times 10^{-11})^{156}$

$= 3.95 \times 10^{-9}$

P_a also represents the probability to induce action potential by a channel.

Quantum tunneling can occur between local and referred neurons where they come close to each other in the posterior (dorsal) root of the spinal cord segment until they reach the dorsal horn (Hall, 2015).Consequently, action potentials carried by local neurons affect the membrane of referred neurons along the course of dorsal root trying to induce an action potential at an area of their membrane available for tunneling. Besides, an action potential induced at an area of neuronal membrane will propagate to adjacent areas (Hall, 2015).

So there will be a probability of inducing action potential P_A in the referred neurons at some point along the course of dorsal root due to quantum tunneling and that induced action potential will eventually propagate through referred neurons and transmitted as a pain signal from the referred area. By using Bernoulli trial equation, I calculate this probability by the following steps:

1. In section 2.3, I assumed that one channel is needed to be tunneled in a surface area of $1\mu m^2$ of neuron membrane to induce action potential and the density of potassium channels is 5 – 50 *channels/*μm^2 with average 28 *channels/*μm^2, so if one of these 28 channels get tunneled, action potential will be induced and propagate to the brain and perceived as referred pain. When two neurons face each other, it is not all of their surface area will be available for tunneling, hence I assume that 10% of their surface area will be available for tunneling and that means only 3 *channels/*μm^2 will get the chance of tunneling. Using Bernoulli trial equation, I calculate the probability of the tunneling P_c of at least one of the 3 *channels/*μm^2 as the following:

   $P_c = 1 - P(0)$

   $= 1 - (1 - P_a)^3$

   $= 1 - (1 - 3.95 \times 10^{-9})^3$

   $= 1.19 \times 10^{-8}$

2. Assuming that dorsal root length is 1cm and the diameter of C-unmyelinated fiber (pain fiber) is $1\mu m$ (Purves *et al.*, 2004), then the surface area available for tunneling $A = 2\pi \times 0.5 \times 10^{-6} \times 1 \times 10^{-2} = 3.14 \times 10^{-8} m^2$ and there is $3.14 \times 10^{-8} m^2 / 1\ \mu m^2 = 3.14 \times 10^4$ areas of 1 μm^2 of referred neurons membrane available for tunneling and I calculate the probability P_A of inducing an action potential in at least one area of the 3.14×10^4 areas that will be enough for action potential propagation and referred pain signal transmission:

   $P_A = 1 - P(0)$

   $= 1 - (1 - P_c)^{3.14 \times 10^4}$

   $= 1 - (1 - 1.19 \times 10^{-8})^{3.14 \times 10^4}$

   $= 3.7 \times 10^{-4}$

Results: The Equation of Referred Pain

Quantum tunneling will occur between the local pain fibers themselves increasing the frequency of action potentials, simultaneously, tunneling will occur between the neurons of the local area and referred area, as a result referred neurons start to acquire a frequency of action potentials increasing with time until reaching a threshold of frequency that makes the patient feels pain in referred area. To calculate the frequency of action potentials in referred neurons, certain considerations should be made first:

1. As in section 2, the probability to induce action potential P_A from the neurons of local area in the neurons of referred area is 3.7×10^{-4} so, if there are 100 neurons in local area ring with 300 action potentials (AP) per second (s) affecting a single neuron in referred area that means the referred neuron will have $100 \times 300 \times 3.7 \times 10^{-4} = 11AP/s$ so as the number of neurons and the frequency increase, the action potential frequency of referred neurons will increase.
2. Transmitting the pain signals from local area to referred area is as following: as time progresses tunneling between local neurons occurs and their frequency of action potentials starts to increase, simultaneously, tunneling occurs between local neurons and referred neurons which they start to acquire increasing frequency of action potentials until reaching a threshold of frequency at which the patient feels pain (Dubin *et al.*, 2009) at referred area.
3. Another types of sensory neurons are present with C-fibers of pain in the dorsal root (Hall, 2015) blocking the tunneling between the local pain fibers themselves and between the neurons of the local and referred areas consequently, the number of neurons participating in tunneling will be less because of blocking, so the area with high density of neurons especially with large myelinated neurons, the more the block will be. In local area there is a block and the fraction of neurons that will participate in tunneling is P_L and if $P_L = 0.1$ that means 10% of neurons will participate in tunneling and the rest will be blocked, also there is a block in referred area P_r preventing tunneling between local and referred neurons.
4. I neglect the effect of quantum tunneling between referred neurons themselves on the frequency of action potentials because it is minimal in comparison with the effect of local neurons since they start with an initial frequency of action potentials while the referred neurons are with no initial frequency.

Now, there is a sequence of steps to derive an equation to describe the referred pain phenomenon based on the previous four points above:

1. The frequency of action potentials in referred neurons F_r is calculated by:

$$F_r = (S_1, S_2, S_3, ..., S_n)P \quad (17)$$

Where $S_1 = N_L f$, $S_n = S_{n-1} + (S_{n-1}P_LP_A)$; N_L is the number of local neurons that can participate in tunneling, f is the initial frequency of action potentials of local neurons and $P = P_LP_rP_A$.

2. Equation (17) represents a mathematic sequence and each element S_n represents the number of action potentials affecting the referred neurons per second and as the sequence progresses this number of action potentials increases, and P represents the fraction of the action potentials that will succeed and induce action potentials in referred neurons. P depends on the block in local area P_L, the block in referred area P_r and the probability of action potential P_A calculated in section 2.4 and n is time in seconds.
3. Now I will derive an equation which calculates the frequency of action potentials in referred neurons at a particular time n depending on the previous points 1 and 2:

$$S_n = S_1, S_1 + (S_1P_LP_A), S_2 + (S_2P_LP_A), S_3 + (S_3P_LP_A), ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1 + (S_1P_LP_A), S_1 + (S_1P_LP_A) + ((S_1 + (S_1P_LP_A))P_LP_A),$$
$$S_2 + (S_2P_LP_A) + ((S_2 + (S_2P_LP_A))P_LP_A, \dots S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1 + (S_1P_LP_A), S_1 + (S_1P_LP_A) + ((S_1 + (S_1P_LP_A))P_LP_A),$$
$$S_2 + (S_2P_LP_A) + ((S_2 + (S_2P_LP_A))P_LP_A, \dots S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1 + S_1P_LP_A, S_1 + 2S_1P_LP_A + S_1(P_LP_A)^2,$$
$$S_2 + (S_2P_LP_A) + ((S_2 + (S_2P_LP_A))P_LP_A, \dots S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2,$$
$$S_2 + (S_2P_LP_A) + ((S_2 + (S_2P_LP_A))P_LP_A, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2,$$
$$(S_2 + (S_2P_LP_A) + S_2P_LP_A + S_2(P_LP_A)^2, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2,$$
$$S_2 + (S_2P_LP_A) + (S_1 + (S_1P_LP_A))P_LP_A$$
$$+ ((S_1 + (S_1P_LP_A))(P_LP_A)^2, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2, S_2 + (S_2P_LP_A) + S_1P_LP_A + S_1(P_LP_A)^2 + S_1(P_LP_A)^2 + S_1(P_LP_A)^3, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2, S_1 + (S_1P_LP_A) + (S_1 + (S_1P_LP_A))P_LP_A + S_1P_LP_A$$
$$+ S_1(P_LP_A)^2 + S_1(P_LP_A)^2 + S_1(P_LP_A)^3, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2, S_1 + S_1P_LP_A + S_1P_LP_A + S_1(P_LP_A)^2 + S_1P_LP_A + S_1(P_LP_A)^2 + S_1(P_LP_A)^2 + S_1(P_LP_A)^3, ...S_{n-1} + (S_{n-1}P_LP_A)$$

$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2, S_1 + S_1(P_LP_A) + S_1(P_LP_A) + S_1(P_LP_A)^2 + S_1(P_LP_A) + S_1(P_LP_A)^2 + S_1(P_LP_A)^2 + S_1(P_LP_a)^3, ...S_{n-1} + (S_{n-1}P_LP_A)$

$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2,$

$S_1 + 3S_1(P_LP_A) + 3S_1(P_LP_A)^2 + S_1(P_LP_A)^3, ...S_{n-1} + (S_{n-1}P_LP_A)$

$= S_1, S_1(1 + P_LP_A), S_1(1 + P_LP_A)^2, S_1(1 + P_LP_A)^3, ...S_1(1 + P_LP_A)^{n-1}$

$= S_1(1, (1 + P_LP_A), (1 + P_LP_A)^2, (1 + P_LP_A)^3, ...(1 + P_LP_A)^{n-1})$

So, $S_n = S_1(1 + P_LP_A)^{n-1}$ and the frequency of action potentials of referred neurons:

$$F_r = S_1P_LP_rP_A(1 + P_LP_A)^{n-1} \qquad (18)$$

Discussion

Now, from equation (18) I can explain the characteristics of referred pain as well as fill the gaps in its theories as the following:

1. As the intensity of local pain increases, the intensity of referred pain increases (Arendt-Nielsen and Svensson, 2001). In the equation, the intensity of local pain is represented by $S_1 = N_Lf$ and the intensity of referred pain is represented by F_r and as S_1 increases, the F_r increases.

2. There is a delay between the onset of local pain and referred pain (Arendt-Nielsen and Svensson, 2001) and it is explained by *n* in the equation. *n* represents the time (in seconds) needed for referred pain neurons to reach an action potential frequency and there is a frequency threshold at which patient starts to feel pain (Dubin *et al.*, 2009) for example if a threshold is 10 AP/s , in the beginning, quantum tunneling might not reach this number of action potentials in the first few seconds, so more time is needed to achieve the threshold.

3. P_A is the probability of inducing action potential and it depends on many factors, as previously explained in section (2) and as the probability of action potential increases, F_r increases. One of the factors that affect P_A is the surface area of neuron membrane and since animal models used in experiments are mice, rats, cats and other small animals (National Research Council, 2012) which are small in comparison to human , that means less surface area available for tunneling and less P_A and eventually, animal models need longer time *n* to reach the threshold of pain and that explains why there is more delay between the onset of local pain and referred pain in animal model than in human (Arendt-Nielsen and Svensson, 2001).

4. Referred pain is often associated with visceral pain which is transmitted through the small unmyelinated C-fibers and it is also called slow pain (Hall, 2015).On the other hand, Fast pain (for example: when the skin is cut with knife or a needle is stuck into the skin) does not radiate to other sites and it is described as sharp and well localized pain (Arome *et al.*, 2014) also, it is transmitted via myelinated Aδ pain fibers. In addition to that, there is a documentation of the presence of referred itching (Evans, 1976) and referred thermal sensations (warmth and cold) (Green, 1978) which are transmitted via unmyelinated C-fibers (Hall, 2015) but there is no documentation in the literature about referred vibration, referred discriminative touch, referred proprioception or referred sterognosis which are transmitted via large myelinated fibers and the reason behind that is slow pain, itching and thermal sensation are transmitted via thin unmyelinated fibers, while the other sensations are transmitted via thick myelinated fibers. In section (2) P_A depends on the length of the barrier; as the length increases, the probability decreases. In the thick fibers, there is a thick myelin sheath that increases the length of the barrier making the probability near zero and consequently, it is unlikely for these sensations to be referred.

5. The slow pain tends to become greater over time (Hall, 2015) and that is attributed to quantum tunneling which occurs between the unmyelinated C-fibers. This will increase the frequency of action potentials over time and consequently the intensity of slow pain.

6. The equation depends more on P_L since there are two of them and one for P_r and that means if local area has low P_L because of high density of thick myelinated fibers, it needs longer and longer time for referred pain to occur making it unobservable and that explains why referred pain is unidirectional (Arendt-Nielsen and Svensson, 2001). So if pain, for example, transmitted from local area of $P_L = 0.9$ to to a referred area of $P_r = 0.1$, the opposite direction (from $P_L = 0.1$ to $P_r = 0.9$) of transmission will need more time making it unobservable.

7. Referred pain and local pain are different in threshold but according to the model of convergent- projection, they should be the same (Arendt-Nielsen and Svensson, 2001) leaving this

model with a defect, but according to the potassium tunneling model; it does not matter the thresholds because what matters is the time needed to reach the threshold of referred pain whatever the thresholds of local and referred pain are.

Conclusion

Potassium tunneling model provides a comprehensive theory to explain referred pain filling the gaps in its theories. In addition, this might set the foundation that quantum mechanics can be integrated in the neuroscience and used to explain many other biological phenomena. Moreover, this might help in explaining the idiopathic and unknown origins of many diseases specifically in the clinical neurology.

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