Inverse neurovascular coupling and associated spreading depolarization models for traumatic brain injury

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Abstract— The paper presents the mathematical model of cortical spreading depolarisation and its effect on inverse neurovascular coupling. The paper considers the potassium ion channels present in the neuron-astrocyte blood vascular network to access the role of potassium ions during spreading depolarisation and associated inverse neurovascular coupling. Simulation of our proposed mathematical model confirms the experimental results that an increase in concentration of potassium ions beyond 20mM in the perivascular space essentially leads to vasoconstriction and hence inverse neurovascular coupling. The propagatory nature of depolarizing potassium waves has been unraveled though our proposed mathematical model.

Keywords: Mathematical modeling, inverse neurovascular coupling, cortical spreading depolarisation, vasoconstriction, spread of depolarisation

I. INTRODUCTION

Cortical spreading depolarisation(CSD) can be characterized by a wave of neuronal inactivity[1] in the brain along with neuronal swelling, dendritic distortions[2] and breakdown of intricate ionic gradients[3] of the major ions namely sodium, potassium and chloride. It represents near to complete electrical silence where the neurons cannot fire action potentials because of sustained depolarisation[4]. CSD is usually found in individuals suffering from aneurism, subarachnoid hemorrhage, migraine, stroke or any kind of traumatic brain injury. It has been observed that in the extracellular space of the neuron, there is a prominent negative change in potential resulting from the gradients of depolarisation along the neuron[5]. One of the most important effects of CSD is the massive changes that it brings about in the cerebral vasculature. These changes however vary among species[6,7].

The most common method for measuring any neuronal activity is to measure the action potential which is also called the firing rate of the neuron. But when cortical spreading depolarisation is at play, the dynamics of the ions are different and this forces the neurons to go through a short period of intense firing and a subsequent period of membrane hyperpolarization. Because of this hyperpolarization the neurons experience electrical silencing and can no longer fire action potential for a period of time, but they gradually recover from this condition. It has been suggested that CSD mainly occurs due to very high concentrations of extracellular potassium ions or glutamate.

Inverse neurovascular coupling, is one of the most prominent effects of cortical spreading depolarisation which is characterized by sudden arteriolar constriction which creates hypoperfusion along with spreading depolarisation[8]. This hypoperfusion not only enhances the detrimental effects of spreading depolarisation but also creates a local deficiency of oxygen and nutrients in the neuronal cells. Deficiency of nutrients and oxygen in the cells due to hypoperfusion leads to a compromise in the cellular metabolism which results in necrosis. This hypoperfusion instigated by the spreading depolarisation not only harms the cells but also prevents recovery of the cells. In a normal cell which is undergoing normal hemodynamic response, an enhancement in cerebral blood flow is observed in response to increased neuronal activity. This response is brought about by the comparative rise of potassium (~10mM) ion concentration, in the perivascular space, which act as vasodilators. However, when the potassium ion concentration rises significantly which usually occurs during spreading depolarisation, the hemodynamic response is inverted and the cerebral blood flow reduces significantly.

Here, the astrocytes play a significant role in recovering the equilibrium concentration of the ions. Situated in between the vascular smooth muscle cells and the neuronal cells, they release potassium ions in the perivascular space through their endfeet. A slight increase in concentration hyperpolarizes the membrane of smooth muscle cells and increases the conductance of the inward rectifier potassium channels. The influx of calcium ions through voltage gated channels also reduces due to hyperpolarization which ultimately leads to vasodilation. When the potassium concentration exceeds 20mM studies have shown that a strong vasoconstrictive effect is observed[9,10,11]. It has been experimentally observed that elevated levels of potassium and decreased
availability of NO leads to a shift spreading hyperemia to spreading ischemia. The propagatory nature of these potassium ions are responsible for the underlying oxygenation, speed and duration of the cortical spreading depolarisation and inverse neurovascular coupling response[12,13]. The astrocytes being mediators maintain the balance of potassium ions with the help of energy dependent ion exchange pumps. Failure to regulate this buffering of potassium ions by the astrocytes is assumed to be the root cause of both spreading depolarisation as well as inverse neurovascular coupling. The Na/K+-ATPase pumps present in both neuronal and astrocytic membrane are responsible for energy dependent uptake of the excess potassium ions to ensure quick restoration of steady state concentration. However, when the inverse neurovascular coupling response is exhibited there is sever ischemia due to vasoconstriction which inhibits the functioning of these active pump and hence prevents easy recovery[11]. This condition can also be described as spreading ischemia where the spreading depolarisation instigates vasoconstriction which creates a change in the cortical slow potential.

In this study we have used the astrocytic potassium channels to create a mathematical model of spreading depolarisation to observe the effects of inverse neurovascular coupling. We have used the potassium channels in the neuron-astrocyte-vascular network system to examine the role of potassium ions in the occurrence of spreading depolarisation and the enhancement of inverse neurovascular coupling. The flow of potassium ions is the basis of our model which has been presented in this paper.

II. Mathematical Model

In order to understand the effects of cortical spreading depolarisation and study the inverse neurovascular coupling response we have divided the system into a 5 compartment model consisting of the neuron, extracellular space, astrocyte, perivascular space and the smooth muscle cells of the cerebral vasculature. The model has been designed here taking into consideration that potassium ions are the basis of these responses. It has been assumed that the sudden rise in the extracellular concentration of potassium ions give rise to the cortical spreading depolarisation which bring about the inverse neurovascular coupling response. Some of the assumptions that we have used in this model are:

1. The volume fractions of the compartments remain constant although some cell swelling occurs during cortical spreading depolarisation.
2. The only sources of potassium ions in the perivascular space(PVS) and the extracellular space(ECS) are the pumps and the ion channels. The ion channels and pumps taken into consideration are the only sources of entry and exit of potassium ions.
3. Only the most relevant ions such as sodium and potassium ions have been taken into consideration and thus only the channels that affect their transport have been described.

Thus the channels described by the model are, the voltage gated potassium channels, the Na+/K+-ATPase pumps of both neurons and astrocytes, the Kir channels present in both vascular cells and astrocytes and the BK channels in the vascular cells.

![Fig. 1: Schematic diagram of the compartments considered in this model](image)

A. Ionic Transport During Neuronal Activities

The potassium ions released into the extracellular space during neuronal activities are mainly brought about by the potassium delayed rectifier current and the transient potassium current. The current flowing through them due to the movement of ions can be estimated by using the Goldman-Hodgkin-Katz equations for active transport. But however active transport is not the only source of potassium ions as there are also leakage channels[14,15]. These leakage currents are estimated using the Hodgkin-Huxley equations. The following equations have been used to describe the active and passive movement of potassium ions from the cells into the extracellular space, where $I_{K^+_{(GHK)}}$ is the current due to active transport, $I_{K^+_{HH}}$ is the current due to passive transport and $V_{K^+}$ is the potential difference.

\[ I_{K^+_{(GHK)}} = m_p h q \frac{g_{K^+} F V_m \left( [K^+]_l - [K^+]_e \exp\left( \frac{-V_m}{\vartheta} \right) \right)}{\vartheta \left[ 1 - \exp\left( \frac{-V_m}{\vartheta} \right) \right]} \]  \hspace{1cm} (1)

\[ \vartheta = \frac{RT}{F} \]  \hspace{1cm} (2)

\[ I_{K^+_{HH}} = g_{K^+} (V_m - V_{K^+}) \]  \hspace{1cm} (3)


\[ V_{K^+} = \varphi \log \frac{[K]_e}{[K]_i} \]  

(4)

**B. Ion Exchange Pumps**

After any kind of neuronal activity, the ionic equilibrium in the extracellular space (ECS) is shifted. The ion exchange pumps present in the neuronal membrane aid in restoration of the steady state to maintain homeostasis. The pumps function by taking in 2 potassium ions inside the cell across the membrane and removing 3 ions of sodium out of the cell. Since this exchange of ions is against the concentration gradient, they require energy to function. ATP is the energy currency of the body which is produced by aerobic respiration in which oxygen is the limiting reagent. Thus oxygen availability is the most important factor when considering the proper functioning of the ion exchange pump. The Na/K-ATPase pump is a transmembrane protein which is an exchange pump present in both neuronal as well as astrocytic membrane and actively aids in recovery of the equilibrium conditions after a depolarisation has occurred. The current due to the ion exchange pumps has been estimated as per the studies conducted by Chang et al[17]

\[ I_{K_{ir}} = \frac{\bar{G}_{K_{ir}} \sqrt{[K^+]}_0 (V_m - V_{K^+})}{1 + \exp\left(\frac{V_m - V_{K,5}}{k}\right)} \]  

(7)

**D. Final equation for the concentration of Potassium Ions**

Thus to conclude the flow of potassium ions through the different channels across the compartmental system we can use the following final equation:

\[ \frac{d[K^+]_{ECS}}{dt} = (I_{K_{ir}}^{(GHK)} + I_{K^+ \text{HH}} - I_{NPump}) \star \frac{1}{f_e F} \]  

(8)

This concentration of potassium ions in the extracellular space will influence the amount of potassium ions taken up by the astrocytes. Thus when estimating the amount of potassium ions taken up by the astrocytes the ECS concentration will act as the initial concentration

Summarizing the above equations, the total potassium concentration released by the astrocytes can be determined by calculating:

\[ \frac{d[K^+]_{AS}}{dt} = (I_{NPump} + I_{K_{ir}}) \star \frac{1}{f_e F} \]

The final concentration of the potassium ions influencing the radius of the vasculature will be the ions taken up by the smooth muscle cells. The main ion channels responsible for taking up potassium ions are the BK channels and the Kir channels present on the surface. Here we are ignoring BK channels as it heavily depends on calcium signaling and does not respond to change in only potassium ion concentration. Thus the final equation is:

\[ \frac{d[K^+]_{PV/C}}{dt} = I_{K_{ir}} \star \frac{1}{f_e F} \]  

(9)

**E. Neurovascular Coupling and change of Vasculature Diameter**
When the potassium ion concentration in the perivascular space is below 10mM it acts as a vasodilator. It elongates the vascular walls so that the cerebral blood flow increases in order to provide for neuronal activity[9,10,11]. But during CSD potassium ion concentration increases beyond the threshold value(20mM) and due to this ionic imbalance vasoconstriction is prevalent. This shift in the hemodynamic response can be traced by estimating the change in the potassium concentration in the perivascular space rise in [K⁺]_{surr}. Cortical spreading depolarisation travels due to diffusion of potassium ions. The propagation of the wave of depolarisation can be estimated by [20]

\[
\frac{d[K^+]_{surr}}{dx} = F([K^+]_{surr}, \omega) + div(D\nabla[K^+]_{surr})
\]

\[
\frac{d[K^+]_{surr}}{dt} = \mu_1([K^+]_{surr} - [K^+]_0) + \mu_2([K^+]_{surr} - [K^+]_0)\omega - \mu_3([K^+]_{surr} - [K^+]_0)\omega
\]

\[
\frac{d\omega}{dt} = G([K^+]_{surr}, \omega)
\]

The simulations were performed by breaking down the model in to one-dimensional ODEs and solved using MATLAB\textsuperscript{®} module pdepe.

The results show a sharp rise in the potassium ion concentration in the perivascular space within a very short amount of time. This observation is at par with the previous experimental studies which show a sudden rise in the extracellular concentration during inverse neurovascular coupling[9,13]. In Fig. 2 it can be observed that the potassium ion concentration in the perivascular space rise to a great extent in a very short amount of time. Due to this rise there is an increase in the storage of intracellular calcium ions in the astrocytes as well as in the smooth muscle cells of the cerebral vasculature. This storage of calcium ions enhances vasoconstriction which leads to a deficiency of oxidative substrates in the neurons. Because of this deficiency of substrates, the cells can no longer generate energy required for their electrical activities. Failure to generate energy results in inactivity of the energy-dependent Na⁺/K⁺-ATPase pumps which are responsible for bringing the extracellular potassium concentration into steady state. Thus the spreading depolarisation persists in that area and inverse neurovascular coupling is also enhanced. This effect can be observed in the Fig. 3.

The change in radius of the vasculature is one of the primary observations of inverse neurovascular coupling. It can be observed in Fig. 4 that the radius increases with increase in concentration because initially potassium acts as a vasodilator. But however as soon as it crosses the threshold of 10mM the hemodynamic response shifts to vasoconstriction. It can be observed that the radius is decreasing with increase in concentration.

The propagation of the depolarisation wave is crucial for understanding as well as coming up with proper therapeutics to counter the harmful effects. The equations of the propagation of potassium ion wave have been solved keeping the boundary conditions into consideration. Here, we have assumed that initially at x=0, [K⁺]= 30mM and ω =0. At x=L(Length of the neuron) ω =1 and \(\frac{d[K^+]_{surr}}{dx} = 1\). The results obtained upon using the model shows an increase in concentration of the potassium ions which is much higher than the normal threshold and with time this wave of change in concentration seems to travel a considerable amount of distance before sharply dropping. In the Fig. 5 it can be observed that at t=10 seconds the rise in concentration is the highest. The concentration rises to as high as 60mM but in the preceding waves of change the concentration seems to reduce. At t=40 seconds the concentration of extracellular potassium is approximately 50mM which is much lower than its earlier counterparts. This increase in concentration seems to remain constant and travels a distance of about 0.9 mm before dropping sharply. This provides relevant proof of the
propagatory nature of the wave of potassium ions. This propagation is assumed to be carried out by diffusion and thus diffusion constants have been used in the equation of propagation. In Fig. 6 and Fig. 7 a 3D contour plot has been performed where the propagation of the wave of potassium ions has been represented with change in time and change in concentration. The first plot shows how initially after the first spiking the concentration is as high as 60mM, much higher than the threshold of 5mM. Since the pumps are dysfunctional due to ischemia the concentration stays high for a considerable amount of time and travels a distance of 0.9mm before dropping slowly. This propagation of the potassium wave shows the spread of the wave of depolarisation after every consecutive spiking. Thus with every spike of neuronal activity the wave of potassium ions travels as much as 0.9mm before a drop in concentration.

Fig. 2: [K+] VS t(time) plot showing the final concentration of [K+] ions in the perivascular space.

Fig. 3: Ipump (Current due to K-Na pump) VS [O2] plot with respect to different [K+] concentration. The exchange pumps rigorously try to bring back the equilibrium [K+] ion concentration but however the concentration is so high that even the pumps are exhausted. Thus the graph depicts how the current of the exchange pumps decreases with increase in [K+] concentration. Because of the reduced blood flow oxygen is scarce which further decapitates these pumps as they are oxygen dependent. Thus a negligible rise in the pump current can also be observed with rise in oxygen.

Fig. 4: r/r0 VS [K+] plot depicting the changes in the blood vessel radius. Normally a slight increase in perivascular space [K+] leads to vasodilation. But during inverse neurovascular coupling the [K+] is much higher than the threshold of 20mM. This causes the blood vessels to constrict rather than dilate which directly reduces the cerebral blood flow. The graph depicts the change in cerebral vasculature where the radius of the blood vessels rises till the [K+] concentration is 10mM which is well within the threshold. But as the concentration rises a sharp decrease in radius is observed.

Fig. 5: A plot depicting the propagation of the wave of depolarisation with increase in concentration.
IV. CONCLUSION

In this model we have traced the flow of potassium ions, during cortical spreading depolarisation, between the nerve cells, astrocytes and the smooth muscle cells of the vascular network. In doing so we studied the effects of inverse neurovascular coupling and how it can affect the neuronal activities. The propagatory nature of potassium ions can be explicitly observed from the results obtained which validates the studies of Gerardo-Giorda et al. and thus provides evidence that the spike in extracellular concentration potassium ions is associated with inverse neurovascular coupling. The study also sheds light on the extent of change in radius of the cerebral vasculature and thus validates the studies conducted by Chang et al. Thus this model was successful in establishing the propagatory nature of the depolarizing wave of potassium ions and it also helps in correlating potassium ion concentration with inverse neurovascular coupling. However, the simplified model that we have shown may be effective in describing the change in vasculature and spread of depolarisation but there are many more intricacies that can make the model more accurate and precise.

This model shows the dependence of the inverse neurovascular coupling response on the potassium ion concentration. Thus future research concentrating on areas such as potassium ion channels in astrocytes and neurons, chemical mediators which activate or deactivate these channels can lead to successful therapeutics. Research targeting on these specific areas can help device novel techniques and methods aiding in treatment of traumatic brain injury patients.

V. APPENDIX

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Name of Parameter</th>
<th>Value of Parameter</th>
<th>Unit</th>
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<td>$I_{\text{max}}$</td>
<td>The Maximum current</td>
<td>0.013</td>
<td>mA/cm$^2$</td>
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<tr>
<td>$E_{\text{m}}$</td>
<td>Membrane potential</td>
<td>-70</td>
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VI. REFERENCES
