Dynamic Mechanism of Epilepsy Generation and Propagation After Ischemic Stroke

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Abstract

Epilepsy is the second largest neurological disease which seriously threatens human life and health. The one important reason of inducing epilepsy is ischemic stroke which causes insufficient oxygen supply from blood vessels to neurons. However, few studies focus on the underlying mechanism of the generation and propagation of epilepsy after ischemic stroke by utilizing modeling methods. To explore the mechanism, this paper establishes a coupled network model consisting of neurons and astrocytes, and introduces a blood vessel to simulate the condition of ischemic stroke. First we study the effect of the degree of vascular blockage on the generation of epilepsy. The results demonstrate that the important reason of epilepsy after ischemic stroke is the disruption of ion concentration gradient. Then we study three factors that influence the epileptic propagation after ischemic stroke: massive glutamate release, excessive receptor activation and high extracellular potassium concentration. The results demonstrate that massive glutamate acting on postsynaptic neurons and the excessive activation of glutamate receptors on postsynaptic neurons promote the epileptic propagation in neuronal population, and massive glutamate acting on astrocytes and excessive activation of metabotropic glutamate receptors on presynaptic neurons inhibit the epileptic propagation, and the potassium uptake by astrocytes suppresses the epileptic propagation. The results are consistent with the experimental phenomena. The simulation results also shed light on the fact that astrocytes have neuroprotective effect. Our results on the generation and propagation of epilepsy after ischemic stroke could offer theoretical guidelines for the treatment of epilepsy after ischemic stroke.

1 Introduction

Epilepsy is a common neurological disease characterized by aberrant firing of neurons[1, 2]. Stroke is an important cause of epilepsy. It is reported that epilepsy patients induced by stroke accounts for about 30-49% of newly diagnosed cases of epilepsy in the aged >65[3, 4], meanwhile epilepsy after stroke further affects the treatment effect of stroke[5, 6]. Generally, there are two kinds of strokes: ischemic stroke and hemorrhagic stroke, the former accounts for 71% of all[7], and 9% of epilepsy patients after stroke are induced by ischemic stroke[8].

Ischemic stroke is mainly caused by the blockage of artery, which decreases blood flow and cerebral metabolic rate for oxygen[9]. Oxygen has essential role in supporting neural firing activity and maintaining ion environment in neuronal system of brain [10, 11]. Metabolic dysfunction induced by ischemic stroke triggers imbalance of ion concentration inside and outside neurons, which is an important cause of epilepsy [12, 13]. Meanwhile, several physiological experiments found that more causes are responsible for the epilepsy after ischemic stroke, including ion channel dysfunction[14], excessive release of neurotransmitters such as glutamate[15], blood-brain barrier destruction[16], and alterations in gene expression[17]. Many physiological studies focused on the probable causes of epilepsy after ischemic stroke but few aimed at the underlying pathogenesis through mathematical modeling methods, especially simulates blood oxygen metabolism in the state of ischemic stroke.

The research of epileptic propagation has been a hotspot. Trevelyan et al. studied the propagation speed of epilepsy by zero magnesium animal model of epilepsy, suggesting that the feedforward inhibition is the prime factor affecting epileptic propagation speed[18]. Khoo et al. proved the generation of epilepsy needs more energy than the one for the propagation process by EEG-fMRI testing method[19]. Reato et al. proposed a network model including of neurons and astrocytes to consider the influence of astrocyte feedback and pulse simulation on the epileptic propagation and found that the balance between excitatory and inhibitory affects the epileptic propagation speed[20]. Martinet et al. studied the effect of extracellular potassium concentration diffusing on the epileptic propagation by developing mean-field model and reproduced the temporal and spatial dynamics of epilepsy[21]. Proix et al. explained the spatiotemporal dynamics of epileptic generation, propagation and termination by constructing a neural field model and verified the conclusion by analyzing the data recording from epileptic patients[22]. But for the moment, no computational model focus on the impact of metabolic dysfunction caused by ischemic stroke on the propagation of epilepsy, especially considering the feedback and regulation of astrocytes.

Astrocytes are the most abundant glial cells which play a fundamental role in maintaining the normal function of the cerebral neural system. Astrocytes can regulate synaptic activity by imposing excitability or inhibitory feedback on neurons after stimulated by neurotransmitter released by neurons[23–25], and regulate the ion concentration in inside and outside neurons, such as buffering the extracellular K^+ concentration by a few ion channels[26]. It's also found that astrocytes play a main role in uptaking extracellular neurotransmitter such as glutamate[27–29]. Based on these characteristics, astrocytes exert positive physiological effects on neurons after ischemic stroke and have a very important neuroprotective effect[30–32]. The above conclusions prove astrocytes can be considered as a new therapeutic target for epilepsy after ischemic stroke. So it's very important to study the effect of astrocytes on epilepsy after ischemic stroke.

In this work, we first built a minimal network model composed of pyramidal neuron, astrocyte, and introduced an updated blood vessel model that simulates the ischemic stroke state. Based on the minimal network model, we studied the underlying mechanism of inducing epilepsy after ischemic stroke. In this part, we mainly studied the effects of vascular blockage and the regulation of extracellular K^+ through astrocyte on neuron firing activity. The numerical results are consistent with the experimental observations[33, 34] and verified the correctness of our model. Then, a coupled population model was developed by connecting 150 pyramidal neurons, 150 astrocytes and a blood vessel. We studied the impact of metabolic dysfunction caused by ischemic stroke on the propagation of epilepsy. Based on experiment results, the effect of the blockage degree of vascular, the massive release of glutamate, the excessive activation of receptors and the high extracellular concentration of potassium on the propagation of epilepsy after ischemic stroke were considered separately. Finally, the potential mechanism of generation and propagation of epilepsy after ischemic stroke were discussed by analyzing the numerical simulation results.

2 Model And Methods

2.1 Membrane potential dynamics

The pyramidal neuron is described by the modified Hodgkin-Huxley model[35–38]. The membrane potential V of neuron are as follows[37]:

$$C\dot{V} = I_{ext} - I_{Na} - I_K - I_{Cl}$$

$$I_{Na} = G_{Na}m^3h(V - E_{Na}) + G_{NaI}(V - E_{Na})$$

$$I_K = G_Kn^4(V - E_K) + G_{KI}(V - E_K)$$

$$I_{Cl} = G_{CIL}(V - E_{Cl})$$

$$\dot{q} = \alpha_q(1 - q) - \beta_qq, q = m, n, h$$

1

where I_{ext} represents external input current, I_{Na} and I_K are sodium and potassium ion currents respectively and containing their respective leakage currents, and I_{Cl} is chloride leakage current. G_{Na} and G_K represent the channel conductance of Na^+ and K^+ . G_{NaI} , G_{KI} and G_{CIL} represent the conductance of the three leak currents. m and n describe the sodium and potassium activation degree, h describes the sodium inactivation, and all vary between 0 and 1. α_q and β_q ($q = m, n, h$) describe the opening and closing probability of ion channels, these parameters are described as follows[39, 40]:

$$\alpha_m = 0.32(54 + V) / \{1 - \exp[-(V + 54)/4]\}$$

$$\beta_m = 0.28(27 + V) / \{\exp[(V + 27)/5] - 1\}$$

$$\alpha_h = 0.128\exp[-(V + 50)/18]$$

$$\beta_h = 4 / \{1 + \exp[-(V + 27)/5]\}$$

$$\alpha_n = 0.032(52 + V) / \{1 - \exp[-(V + 52)/5]\}$$

$$\beta_n = 0.5\exp[-(V + 57)/40]$$

2

In equation 1, E_{Na} , E_K and E_{Cl} represent the equilibrium potential of Na^+ , K^+ and Cl^- that dependent on Nernst equations, as follows:

$$E_{Na} = 26.64\ln\left(\left[Na^+\right]_o / \left[Na^+\right]_i\right)$$

$$E_K = 26.64 \ln \left(\left[K^+ \right]_o / \left[K^+ \right]_i \right)$$

$$E_{Cl} = 26.64 \ln \left(\left[Cl^- \right]_i / \left[Cl^- \right]_o \right)$$

3

where $[s]_o$ and $[s]_i$ ($s = Na^+, K^+, Cl^-$) are ion concentration inside and outside the neuron respectively, and the ion concentrations are changing with neuronal activity except chloride concentration.

2.2 Ion concentration dynamics

In the model, ions concentration are changed follow neuronal activity. $\left[K^+ \right]_o$ is influenced by K^+ currents (I_K), Na^+-K^+ pumps (I_{pump} from neuron, $I_{gliapump}$ from glia), diffusion of K^+ from interstitial volume (I_{diff}), and uptake by glial cell (I_{glia}) [35, 37], the specific form of $\left[K^+ \right]_o$ is as follows:

$$\left[K^+ \right]_o = 0.0445\beta I_K - 2\beta I_{pump} - I_{diff} - I_{glia} - 2I_{gliapump}$$

4

where β is the ratio of the intracellular volume to the outer volume. We supposed the quantity of Na^+ into the cell is equal to K^+ out of the cell, so $\left[K^+ \right]_i$ can be described as:

$$\left[K^+ \right]_i = 140\text{mM} + (18\text{mM} - \left[Na^+ \right]_i)$$

5

$\left[Na^+ \right]_i$ is determined by Na^+ currents (I_{Na}) and Na^+-K^+ pumps, and $\left[Na^+ \right]_o$ are updated based on $\left[Na^+ \right]_i$, the specific form of $\left[Na^+ \right]$ are as follows:

$$\left[Na^+ \right]_i = -0.0445I_{Na} - 3I_{pump}$$

$$\left[Na^+ \right]_o = 144\text{mM} - \beta(\left[Na^+ \right]_i - 18\text{mM})$$

6

The Na^+-K^+ pumps (I_{pump} from neuron, $I_{gliapump}$ from glia) are modeled by:

$$I_{pump} = \frac{\rho}{1 + \exp\left[\left(25 - [Na^+]_i\right)/3\right]} \times \frac{1}{1 + \exp(5.5 - [K^+]_o)}$$

$$I_{gliapump} = \frac{1}{3} \frac{\rho}{1 + \exp\left[\left(25 - [Na^+]_{gi}\right)/3\right]} \times \frac{1}{1 + \exp(5.5 - [K^+]_o)}$$

7

where

$$\rho = \rho_{max} / (1 + \exp[(20 - [O_2]_o)/3])$$

8

where ρ is Na^+-K^+ pump rate which is updated based on extracellular oxygen concentration ($[O_2]_o$).

The ability of glial cell handling $[K^+]_o$ is modeled by:

$$I_{glia} = G_{glia} / (1 + \exp[(18 - [K^+]_o)/2.5])$$

9

where G_{glia} is the glial uptake rate of $[K^+]_o$. The diffusion of K^+ from interstitial volume (I_{diff}) is modeled by:

$$I_{diff} = \epsilon_k ([K^+]_o - [K^+]_{ves})$$

10

where ϵ_k is K^+ diffusion constant, and $[K^+]_{ves}$ represents $[K^+]$ in blood vessel.

2.3 Oxygen concentration dynamics

In the work, we introduced and modified the blood vessel model[41], so that it can simulate blood oxygen metabolism in the state of ischemic stroke. The specific form of the blood vessel model are as follows:

$$BFlow = \eta BFlow_{ves}$$

$$OEF = (OEF_{ave} - OEF_{var} \tanh(\frac{BFlow - 0.7}{0.4}) - OEF) / \tau_{OEF}$$

$$[O_2]_{ves} = OEF * BFlow * [O_{ini}]$$

11

where $BFlow$ represents blood flow in blood vessel, η describes the blockage degree of the blood vessel ($\eta=1$ when the blood vessel in healthy state and $\eta=0$ when the blood vessel is completely concluded), and $BFlow_{ves}$ represents maximum blood flow in healthy blood vessel ($BFlow_{ves}=1$). OEF is oxygen extraction factor, OEF_{ave} is normal oxygen extraction factor, OEF_{var} represents the maximum possible variation of OEF , and τ_{OEF} is an adaptation time that OEF adapt to $BFlow$ changes. $[O_2]_{ves}$ represents the concentration of oxygen supplied to the neuron by blood vessel, Figure 1 describes the oxygen concentration $[O_2]_{ves}$ varies with the blockage degree of the blood vessel η , and $[O_{ini}]$ represents the normal oxygen concentration in healthy blood vessel. The extracellular oxygen concentration ($[O_2]_o$) is modeled by:

$$[O_2]_o = -\alpha (I_{pump} + I_{gliapump}) + \epsilon_o ([O_2]_{ves} - [O_2]_o)$$

12

where α is a conversion factor from changing current to oxygen concentration[37]. ϵ_o is diffusion rate of oxygen.

2.4 Coupled population model

To study the propagation of epilepsy, we built a coupled population model based on the simple network model and consider the astrocyte feedback, including 150 pyramidal neurons, 150 astrocytes and a blood vessel. In the model, pyramidal neurons are connected by synapses, and astrocytes are connected by gap junctions, pyramidal neurons and astrocyte cells are connected with the bidirectional feedback, and equal concentration of oxygen are transported to every neurons and astrocytes by blood vessel. The schematic of model is shown in Figure 2. In this model, the membrane potential V of neuron is changed as follows:

$$C\dot{V} = I_{Na} - I_K - I_{Cl} - I_{syn} - I_{as}$$

13

where

$$I_{syn} = g_{se}(V - V_e)s$$

14

where I_{syn} represents synaptic current, g_{se} describes the activation level of glutamate receptors on the postsynaptic neuron, and V_e is reversal potential of synapse. The synaptic input s from previous pyramidal neuron is modeled by:

$$[T]_{i-1} = \frac{1}{1 + \exp\left(-\frac{V+9}{8}\right)}$$

$$\dot{s}_i = 5p_{neu}[T]_{i-1}(1 - s_i) - s_i$$

15

where $[T]_{i-1}$ represents the released neurotransmitter by the $i - 1$ th neuron, since pyramidal neurons are excitatory neurons, the neurotransmitter released is mainly glutamate, so $[T]_{i-1}$ refers to glutamate in the model. p_{neu} represents the synaptic input intensity to postsynaptic neuron.

In coupled population model, $[K^+]_o$ also is influenced by the K^+ diffusion from neighboring neurons, the specific form of the lateral diffusion term is as follows:

$$I_{lat} = \frac{D_k}{\Delta x^2}([K^+]_o^{i-1} + [K^+]_o^i + [K^+]_o^{i+1} - 3[K^+]_o^i)$$

16

where D_k is the potassium diffusion coefficient, and Δx is the distance between two neurons. So the final manifestation of $[K^+]_o$ is as follows:

$$[K^+]_o = 0.0445\beta I_K - 2\beta I_{pump} - I_{diff} - I_{glia} - 2I_{gliapump} + I_{lat}$$

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The binding neurotransmitters to receptors on adjacent astrocytes will cause the astrocytes to produce IP_3 , and eventually cause the concentration of Ca^{2+} increasing in astrocytes. In order to describe this process, we introduced the improved Li-Rinzel model[42–44] as follows:

$$\dot{[IP_3]} = \frac{([IP_3^*] - [IP_3])}{\tau_{ip_3}} + r_{ip_3}p_{as}[T] + k_g([IP_3]_{i+1} + [IP_3]_{i-1} - 2[IP_3]_i)$$

$$[Ca^{2+}] = J_{chan} + J_{leak} - J_{pump}$$

$$\dot{q} = \alpha_q(1 - q) - \beta_q q$$

18

where

$$J_{chan} = c_1 V_1 p_\infty^3 n_\infty^3 q^3 \left([Ca^{2+}]_{ER} - [Ca^{2+}] \right)$$

$$J_{leak} = c_1 V_2 \left([Ca^{2+}]_{ER} - [Ca^{2+}] \right)$$

$$J_{pump} = \frac{V_3 [Ca^{2+}]^2}{[Ca^{2+}] + k_3^2}$$

19

where

$$\begin{aligned} p_{\infty} &= \frac{\left[IP_3 \right]}{\left[IP_3 \right] + d_1} \\ n_{\infty} &= \frac{\left[Ca^{2+} \right]}{\left[Ca^{2+} \right] + d_5} \\ \alpha_q &= a_2 d_2 \frac{\left[IP_3 \right] + d_1}{\left[IP_3 \right] + d_3} \\ \beta_q &= a_2 \left[Ca^{2+} \right] \\ \left[Ca^{2+} \right]_{ER} &= \frac{c_0 - \left[Ca^{2+} \right]}{c_1} \end{aligned}$$

20

where $[IP_3]$ is the IP_3 concentration in astrocyte cytosolic, $[IP_3]^*$ is the balanced concentration of IP_3 , $a_n d$ represents the intensity of synaptic input to neighboring astrocyte, k_g refers to the coupling coefficient of astrocyte gap junctions. $[Ca^{2+}]$ is the Ca^{2+} concentration in astrocyte cytosolic, J_{chan} and J_{leak} refer to Ca^{2+} flow and leakage flow from endoplasmic reticulum (ER) to cytosol, and J_{pump} refers to the pump flow from ER to cytosol. $[Ca^{2+}]_{ER}$ is the Ca^{2+} concentration in astrocyte ER.

When $[Ca^{2+}]$ exceeds a threshold, astrocytes release gliotransmitters into synapses to regulate neuronal activity. According this process, a dynamical variable f is introduced to picture the astrocyte feedback[44] which has the following form:

$$\dot{f} = \frac{-f}{\tau_{Ca^{2+}}} + (1 - f) \kappa \Phi \left[Ca^{2+} \right] - \left[Ca^{2+} \right]_{th}$$

and combine the strength of the astrocyte feedback $\{\lambda\}$ which describes the activation of the metabotropic glutamate receptors on the presynaptic neuron, a final equation about astrocyte feedback current is described as follow:

$$I_{as} = \lambda f$$

22

The bidirectional feedback between astrocytes and neighbor neurons is achieved by “tripartite synapse” which consist of pre- and postsynaptic neurons and astrocyte [45–47]. It’s reported that gliotransmitters inhibit the release of neurotransmitters when gliotransmitters act on presynaptic neurons and inhibit synaptic activity [48, 49]. So in the model, the astrocyte feedback is inhibitory.

2.5 Methods

We integrated the model numerically using Euler method with a fixed time step of 0.08 ms, the total calculation time was 1500s. Considering the simulation accuracy, the first 160s was abandoned. And the values of various parameters used in the model are shown in Table 1.

3 Numerical Results And Discussion

3.1 Epilepsy dynamics induced by ischemic stroke in minimal network model

3.1.1 The effect of η on the generation of epilepsy

It’s convinced that abnormal ion concentration of intra- and extra- cellular space caused by ischemic stroke, especially potassium ion, affecting the excitation of neurons and even induces epilepsy [50, 51]. Therefore, we first study the effect of blood vessel blockage on $\{K^+\}_o$ to investigate the mechanism of epilepsy after ischemic stroke in the minimal network model. The result is shown in Figure 3.

Figure 3 (a) shows the maximum and minimal extracellular potassium ion $\{K^+\}_o$ in related to blockage degree η , and Figure 3 (b) - (d) show the time series of membrane potential V (blue line) and extracellular potassium ion $\{K^+\}_o$ (red line) for $\eta = 0.5, 0.36$ and 0.2 , respectively. From Figure 3 (a), we observe that as η decreases, $\{K^+\}_o$ changes from slight oscillations (see Figure 3 (a), inset) to huge oscillations, and finally tends to rest. The oscillations of $\{K^+\}_o$ affect neuronal activity. In $\eta = 0.5$, the neuron fire normally and $\{K^+\}_o$ in slightly oscillations because of sufficient blood oxygen supply (Figure 3 (b)). In $\eta = 0.36$, insufficient blood oxygen leads to inhibition of the activity of the sodium-potassium pump [13, 37], making it unable to fast enough to adjust the concentration gradient of intracellular and extracellular

ions, causing $\left\{K^+\right\}_o$ fluctuates in large region (shown in Figure 3 (a) and (c)), and further induces the neuron epileptic-like firing (shown in Figure 3 (c)), the epileptic-like firing form is similar to the epileptic firing recorded in the experiment[33], the region of $\left\{K^+\right\}_o$ oscillations also is similar to experimental results[52]. At $\eta = 0.2$, the sodium-potassium pump strength is too weak to support neuron firing, leading to the neuron to fall into rest state and so does $\left\{K^+\right\}_o$, the details are shown in Figure 3 (a) and (d). In order to show the variation characteristics of V and $\left\{K^+\right\}_o$, we used different time scales in Figure 3 (b) - (d).

These results suggest that blood oxygen is crucial to neuron activity, and insufficient blood oxygen induced by ischemic stroke can cause epilepsy. The results verify the experimental observation that hypoxia in a certain concentration range can induce epilepsy[33].

3.1.2 The effect of $\{G\}_{glia}$ on epilepsy dynamics

Besides of the sodium-potassium pump adjusting, astrocyte potassium uptake is also very important for extracellular potassium homeostasis [26, 36, 53, 54]. In this section, we investigate the effect of the astrocyte potassium uptake on neuron firing activity used the minimal network model.

Figure 4 (a) shows the change of $\left\{K^+\right\}_o$ with $\{G\}_{glia}$, which is the astrocyte uptake rate of $\left\{K^+\right\}_o$, the results are plotted in Figure 4 (a) for $\{G\}_{glia}=6, 8$ and 10 . The two small figures are the neuron membrane potential V corresponding to $\{G\}_{glia}=6$ and 10 , respectively. From the figure 4 (a), we observe the peak value and range of $\left\{K^+\right\}_o$ drops with the increase $\{G\}_{glia}$, and the firing state from epileptic-like firing (small figure (1) in figure 4 (a), $\{G\}_{glia}=6$) to normal firing (small figure (2) in figure 4 (a), $\{G\}_{glia}=10$). The results show that $\left\{K^+\right\}_o$ decreases gradually as the increase of the strength of astrocyte potassium uptake, resulting in the reduction of neuronal excitability and transition of neuron firing state. Figure 4 (b) shows that the neuron firing frequency in single epileptic-like firing event decreases with the increase of $\{G\}_{glia}$, which indicates neuronal excitability decreasing as potassium uptake of astrocyte enhanced.

The results demonstrate that astrocyte could adjust neuronal excitability and influences epilepsy dynamics in neuron by taking extracellular potassium which is consistent with the experiment results that astrocyte affects neuronal epilepsy by regulating extracellular potassium[34].

The comparison between the above numerical simulation results and related experimental results proves the correctness of the model and simulation results.

3.2 Epilepsy dynamics induced by ischemic stroke in coupled population model

3.2.1 The effect of η on the generation and propagation of epilepsy

In the 3.1 section, we used the minimal neuron-astrocyte-blood vessel network model to study the impact of η and $\{G\}_{\text{glia}}$ on epilepsy dynamics in single neuron. In the following research, we will study the generation and development of the epilepsy after ischemic stroke at network level. Firstly, we investigate the effect of η on the generation of epilepsy in neuronal population with synaptic conductance $\{g\}_{\text{se}} = 0.145$ and the strength of the astrocyte feedback $\{\lambda\} = 0$ (without the astrocyte feedback), and we select the time period from 480s to 1280s for more intuitive research.

Figure 5 (a), (c) and (e) show the time series of neuronal network firing for $\eta = 0.5, 0.36$, and 0.2 , respectively, and the 50th neuron is selected to show the firing state as Figure 5 (b), (d) and (f). As seen in Figure 5 (a), when $\eta = 0.5$, neuronal population fire normally because of sufficient blood oxygen supply, and the firing state of the 50th neuron is given in Figure 5 (b). But with the decrease of η , the firing state changes to epileptic-like firing (Figure 5 (c), $\eta = 0.36$) and the epilepsy spread to the tail of the neuronal population because the limited blood oxygen supply weakens the ability of synaptic transmission, and the detail of epileptic-like firing is shown in Figure 5 (d). When η is further reduced, neuronal population go to rest state (Figure 5 (e), $\eta = 0.2$) because the blood oxygen too limited to maintain neuronal firing, and the detail of rest state is shown in Figure 5 (f).

The results confirm that ischemic stroke can trigger the generation and propagation of epilepsy. In the following research the value of η is set to 0.36 to simulate the condition of ischemic stroke.

3.2.2 The effect of abnormal neurotransmitter release on epileptic propagation

Studies have shown that ischemic stroke leads to the release of a large amount of excitatory neurotransmitter glutamates, which significantly influences the excitability of neurons [55, 56]. For simulating the blood blockage caused by ischemic stroke, the value of η is set to 0.36 and the increase of the synaptic input intensity to postsynaptic neurons $\{p\}_{\text{neu}}$ and the synaptic input intensity to astrocytes $\{p\}_{\text{as}}$ are used to simulate the effect of the massive release of glutamates on neurons and astrocytes, respectively.

The effect of $\{p\}_{\text{neu}}$ on epileptic propagation are shown in Figure 6 with $\{p\}_{\text{as}} = 1$. From Figure 6 (a), we observe the synaptic current $\{i\}_{\text{syn}}$ (the averaged synaptic current at epileptic firing times) received by each neuron in neuronal population gradually increases as $\{p\}_{\text{neu}}$ increases from 1.00 to 1.24 (Figure 6 (a)), the reason is the increase of excitatory neurotransmitter glutamates in synapse enhances the excitability of neurons. The increase of synaptic current leads to a gradual raise in the network activation of the neuronal population (network activation refers to the proportion of the number of firing neurons to all neurons in neuronal population, which is averaged value of the network activation at epileptic firing times) (Figure 6 (b)), and eventually cause more neurons are recruited to epileptic-like firing (Figure 6 (c)) and the propagation speed of epilepsy also is enhanced (Figure 6 (d)), the region of the propagation speed is compatible with experimental evidence[57]. The specific examples of the effect of abnormal neurotransmitter release on epileptic propagation are shown in Figure 6 (e) for $\{p\}_{\text{neu}} = 1$ and

Figure 6 (f) for $\{p\}_{\text{neu}} = 1.24$, the epileptic propagation distance (number of recruited neurons) obviously increases as $\{p\}_{\text{neu}}$ increases.

These results confirm that the massive release of glutamate caused by ischemic stroke strengthens the distance and speed of epileptic propagation.

Figure 7 shows Astrocytes suppress synaptic activity by imposing inhibitory feedback on presynaptic neurons after stimulated by neurotransmitter released by neurons[48, 49]. Utilizing this feedback, astrocytes can more strongly participate in the regulation of synaptic transmission under condition of an increase of glutamate caused by ischemic stroke. As seen in Figure 7 (a), the astrocyte feedback current $\{I\}_{\text{as}}$ received by each neuron in neuronal population gradually increases as $\{p\}_{\text{as}}$ increases from 1.00 to 1.20. And the increase of astrocyte feedback current suppresses the activity of presynaptic neuron, resulting in a gradual reduction in the release of glutamate in the synapse (Figure 7 (b)). The reduction in releasing glutamate means the synaptic activity is suppressed, which ultimately leads to the number of neurons with epileptic-like firing is reduced (Figure 7 (c)), and with slower the propagation speed of epilepsy (Figure 7 (d)).

The results demonstrate astrocytes restrain epileptic propagation by inhibiting synaptic transmission during ischemic stroke, and play an important neuroprotective role.

In the above two section, we separately studied the effect of increased glutamate acting on neurons and astrocytes on epilepsy propagation. In this section, we simultaneously consider the effect of increased glutamate acting on neurons and astrocytes on epilepsy propagation in neuronal population under the competition between the two influences. The results are shown in Figure 8. Figure 8 (a) and (b) show the number of neurons with epileptic-like firing and the propagation speed of epilepsy change with the increase of $\{p\}_{\text{as}}$ and $\{p\}_{\text{neu}}$ simultaneously. From Figure 8 (a) and (b), we can clearly observe that when $\{p\}_{\text{neu}}$ and $\{p\}_{\text{as}}$ increase at the same time, the number of neurons with epileptic-like firing and the propagation speed of epilepsy increase significantly. The results prove that the release of massive of glutamate caused by ischemic stroke can promote the propagation of epilepsy, and the protective effect of astrocytes can only relatively inhibit the propagation of epilepsy but cannot prevent it.

The results in the section indicate that the massive release of glutamate caused by ischemic stroke promotes the propagation of epilepsy by enhancing the synaptic current, while the feedback effect of astrocytes inhibit synaptic transmission and thus suppress the propagation of epilepsy, which proves the neuroprotective effect of astrocytes, but this effect is limited and cannot prevent the generation and propagation of epilepsy.

3.2.3 The effect of abnormal receptor activation on epileptic propagation

Ischemic stroke not only affects the release of neurotransmitters, but also causes changes in pre- and post-synaptic receptors. Studies have shown ischemic stroke leads to excessive activation of glutamate

receptors in postsynaptic neurons[58, 59] and massive activation of metabotropic glutamate receptors in presynaptic neurons[60, 61], and induces epilepsy. For simulating the blood blockage caused by ischemic stroke, the value of η is set to 0.36, and the synaptic conductance $\{g\}_{se}$ and the strength of the astrocyte feedback $\{\lambda\}$ are used to depict the activation levels of glutamate receptors in postsynaptic neurons and metabotropic glutamate receptors in presynaptic neurons.

The effect of $\{g\}_{se}$ on epileptic propagation is shown in Figure 9 with $\{\lambda\} = 0$, and the synaptic conductance $\{g\}_{se}$ describes the activation level of glutamate receptors on the postsynaptic neurons. Excessive activation of glutamate receptors causes more glutamate to act on postsynaptic neurons and affect neuronal firing activity. As shown in Figure 9 (a), the synaptic current $\{I\}_{syn}$ in neuronal population gradually increases as $\{g\}_{se}$ increases from 0.145 to 0.151. The increase in synaptic current strengthens the network activation (Figure 9 (b), as $\{g\}_{se}$ gradually increases from 0.145 to 0.152), which is consistent with related experimental and modeling studies[42, 62]. The increase of $\{g\}_{se}$ reinforces the connection among neurons in neuronal population and eventually promotes epileptic propagation. Figure 9 (c) shows more neurons are recruited to epileptic-like firing with the $\{g\}_{se}$ growing, and Figure 9 (d) shows that the speed of epileptic propagation is strengthened with the increase of $\{g\}_{se}$.

The results indicate that the increasing $\{g\}_{se}$ improves the excitability of neuronal population by raising the synaptic current and promotes epileptic propagation.

The effect of $\{\lambda\}$ on epileptic propagation is shown in Figure 10 with $\{g\}_{se} = 0.145$, and the strength of the astrocyte feedback $\{\lambda\}$ actually describes the activation level of the metabotropic glutamate receptors on the presynaptic neuron. In the bidirectional feedbacks between neurons and astrocytes, the astrocytic glutamate acting on metabotropic receptors at presynaptic neurons affects calcium ions into the neurons and thereby suppressing synaptic transmission[61]. As shown in Figure 10 (a), the astrocyte feedback current $\{I\}_{as}$ gradually increases as $\{\lambda\}$ increases from 0.01 to 0.07. The increase of $\{I\}_{as}$ suppresses the activity of presynaptic neurons, resulting in a decrease in glutamate release (Figure 10 (b), with $\{\lambda\}$ gradually increases from 0.01 to 0.07. Contrary to the promotion effect of $\{g\}_{se}$, astrocytes suppress epileptic propagation utilizing the effect of presynaptic inhibition. Figure 10 (c) shows fewer neurons are recruited to epileptic-like firing as $\{\lambda\}$ increases, Figure 10 (d) shows the propagation speed of epilepsy is reduced with the increase of $\{\lambda\}$.

The results demonstrate that astrocytes can weaken the synaptic transmission by suppressing the excitability of presynaptic neurons and undermine epileptic propagation.

The results in this section indicate that the excessive activation of postsynaptic glutamate receptors caused by ischemic stroke can enhance the excitability of post-synaptic neurons by enhancing the synaptic transmission, which is conducive to the propagation of epilepsy in the neuronal population. And excessive activation of metabotropic glutamate receptors inhibits synaptic transmission by weakening the excitability of presynaptic neurons, thereby inhibiting epileptic propagation. It also reflects the self-regulation and mutual influence of the nervous system.

3.2.4 The influence of astrocyte potassium uptake on epileptic propagation

It's reported that astrocyte potassium uptake plays a very important role in removing extracellular potassium[26, 53, 54], and this effect becomes more pronounced during ischemic stroke process. The increase in $\{K^+\}_o$ caused by ischemic stroke stimulates the increase in potassium uptake capacity of astrocytes, thereby inhibiting neuronal excitability and reducing neuronal damage[63]. For simulating the blood blockage caused by ischemic stroke, the value of the blockage degree of the blood vessel η is set to 0.36, and $\{G\}_{glia}$ is used to depict the potassium uptake capacity of astrocytes.

Figure 11 (a) reports extracellular potassium concentration $\{K^+\}_o$ changes with $\{G\}_{glia}$, it can be observed that $\{K^+\}_o$ gradually decreases as $\{G\}_{glia}$ increases from 3.0 to 8.0, the specific example is shown in Figure 11 (b). In Figure 11 (b), the time series of $\{K^+\}_o$ in the 50th neuron in the neuronal population are listed with $\{G\}_{glia} = 3$ (black line), 5.5 (red line) and 8 (blue line), respectively. It can be seen that $\{K^+\}_o$ decreases with the increase of $\{G\}_{glia}$, and the duration of $\{K^+\}_o$ maintaining a high level is shrinking. The reason is the capacity of astrocytes removing extracellular potassium continues to be enhanced with the increase of $\{G\}_{glia}$. The decline of $\{K^+\}_o$ alleviates the excitability of presynaptic neurons, leading to the decrease of synaptic current $\{I\}_{syn}$, (Figure 11 (c))with $\{G\}_{glia}$ gradually increases from 3.5 to 8.0, and then reduces the firing frequency (firing frequency refers to the number of neuron firing per second in each epileptic-like firing event in neuronal population, which is averaged value of the firing frequency at all chosen epileptic-like firing events) of postsynaptic neurons (Figure 11 (d), $\{G\}_{glia}$ gradually increases from 3.0 to 8.0), eventually causes less neurons are recruited to epileptic-like firing (Figure 11 (e)) and the speed of epileptic propagation is reduced (Figure 11 (f)).

The results confirm that extracellular potassium concentration significantly influences the excitability of neurons and astrocytes play a very important role in removing extracellular potassium. Due to the scavenging effect of extracellular potassium by astrocytes, the epileptic propagation is effectively weakened.

4 Conclusion

Epilepsy after ischemic stroke seriously affects people's health and quality of life, so that it's very important to study its pathogenesis and propagation in the neuronal network. Few work investigated the pathogenesis and propagation of epilepsy after ischemic stroke by utilizing modeling methods. In this work, we constructed a minimal network model consisting of neuron, astrocyte, and a vessel model. By utilizing the minimal model, we investigated the underlying mechanism of epilepsy after ischemic stroke. And based on the minimal model, we constructed a coupled network model including neuronal population, astrocytes population and a blood vessel to study the propagation characteristics of epilepsy after ischemic stroke, and considered the feedback and regulation of astrocytes.

First, we studied the effects of the blockage degree of the blood vessel and the potassium uptake ability of astrocyte on the generation of epilepsy after ischemic stroke in minimal network model. The results showed that ischemic stroke can trigger the generation of epilepsy, and the disruption of ion concentration gradient is an important reason. The specific reason is that the insufficient blood oxygen induced by ischemic stroke cannot meet the demands of sodium-potassium pump to restore the ion concentration gradient, resulting in the imbalance of ion concentration inside and outside the neuron.

Secondly, we studied the effect of the massive release of glutamate caused by ischemic stroke on epileptic propagation. The results showed that the massive release of glutamate acting on different cell leads to opposite effect, and highlighted the neuroprotective effect of astrocytes. Excessive glutamates acting on post-synaptic neurons could promote the propagation of epilepsy in neuronal population by increasing the synaptic transmission. But on the contrary, excessive glutamates act on astrocytes will inhibit epileptic propagation by inhibiting neurotransmitter transmission. And under the competition between the two effects, the massive release of glutamate still strength epileptic propagation. The result verified that ischemic stroke can induce epilepsy in real state.

Thirdly, we studied the influence of excessive activation of glutamate receptors in postsynaptic neurons and metabotropic glutamate receptors in presynaptic neurons caused by ischemic stroke on the propagation of epilepsy after ischemic stroke. The results showed that the former enhances the propagation of epilepsy after ischemic stroke by strengthening synaptic transmission, and the latter showed the opposite effect by inhibiting the excitability of presynaptic neurons through astrocyte feedback, which illustrates the neuroprotective effect of astrocytes.

Finally, by analyzing the effect of the potassium uptake of astrocytes on epileptic propagation, we revealed the abnormal increase of extracellular potassium concentration not only induces epilepsy but also promotes its propagation, and the high capacity of potassium uptake of astrocytes can weaken epileptic propagation.

In this study, by constructing neuron-astrocyte-blood vessel coupled network model, we mainly investigated four factors which influence the generation and propagation of epilepsy after ischemic stroke: the blockage degree of vascular, massive glutamate release, excessive receptor activation and high extracellular potassium concentration. Our findings revealed the potential mechanism of generation and propagation of epilepsy after ischemic stroke, and highlighted the neuroprotective effect of astrocytes. It also provides a deeper understanding of the important role of blood oxygen in neuronal firing activities. It's helpful to formulate new strategies for the treatment of epilepsy after ischemic stroke.

Declarations

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Data availability The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest The authors declare that they have no conflict of interest.

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Tables

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Figures

Figure 1

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Figure 2

Coupled population model of neurons, astrocytes and a blood vessel. PY and As represent pyramidal neurons and astrocytes, respectively. The red filled

circles represent blood oxygen. Neurons are connected by excitatory synapses, astrocytes are connected by gap junctions, and the bidirectional feedback are represented by double arrow. The unidirectional arrows from the blood vessel represent the blood oxygen supply to each cell.

Figure 3

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Figure 4

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Figure 11

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