REVIEW

Astrocyte and ions metabolism during epileptogenesis: A review for modeling studies*

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(Received 22 October 2019; revised manuscript received 23 December 2019; accepted manuscript online 9 January 2020)

As a large group of cells in a central nervous system, astrocytes have a great influence on ion and energy metabolism in a nervous system. Disorders of neuronal ion and energy metabolism caused by impaired astrocytes play a key role in the pathogenesis of epilepsy. This paper reviews the existing computational models of epileptogenesis resulting from impaired astrocytes and presents several open perspectives with regard to ion and energy metabolism-induced epileptogenesis in a neuron-astrocyte-capillary coupled model.

Keywords: epileptogenesis, astrocyte, potassium, glutamate

PACS: 87.19.lk, 87.19.ll, 87.19.L–, 87.19.lj **DOI:** 10.1088/1674-1056/ab6961

1. Introduction

Epilepsy is the second most common brain disorder. It has been reported that 40% of the world's epileptic population suffers from refractory epilepsy that is resistant to current anti-epileptic drugs. The main reason is that a poor understanding of the pathogenesis of various types of epilepsies leads epileptic activities to be controlled insufficiently.[1,2] Therefore, there is an urgent need to understand the underlying mechanism of epilepsy to prevent the epileptogenesis and improve treatments in individuals that already suffered from it.[3,4]

To date, many researchers have studied the mechanism of epileptogenesis. Early researchers mainly focused on pathological discharges of a single neuron and neural populations caused by abnormal ion channels in neurons.[5–7] For example, the brain discharge rhythm of epileptic patients from the perspective of nonlinear dynamics has been studied.[8–11] In 2001, research published in *Nature Neuroscience* revealed that astrocytes are directly involved in neuronal discharges rather than providing support and nutrition to neurons, as one long thought. This article was a milestone in the study of the normal and pathological functions of the nervous system from the perspective of neuronal-astrocyte networks.[12] In recent years, many studies have shown that astrocytes are directly involved in epileptogenesis in the nervous system. For example, astrocytes inhibit the generation of high-potassium epilepsy by buffering extracellular potassium ions.[13–15] Additionally, astrocytes can increase the probability of epilepsy by releasing glutamate into the extracellular space.[15,16] In 2018, Ohno proposed that the negative effects of alternative drugs on neurons on the human brain, astrocyte would be a novel target for the further treatment of epilepsy with drugs.[17] Therefore, the study of how astrocytes regulate extracellular ions and neurotransmitters can provide theoretical support for anti-epileptic strategies from the perspective of ion metabolism in astrocytes. In addition, many researchers have discovered that astrocytes regulate neuronal discharges by metabolizing glucose absorbed from capillaries,[18–20] which may provide a new perspective on the phenomenon of epileptic dilation caused by energy depletion.

This review surveys the existing researches of epileptogenesis modulated by impaired astrocytes and provides a view of computational models of astrocyte voltage to better understand how astrocyte voltage interacts with neuronal firing during epilepsy. Epilepsy involves not only hyper-synchronization of collective neuronal activity but also a series of astrocyte and glucose activities.[19] Hence, we also provide an outlook on how astrocytes promote the spread of epilepsy through energy metabolism.

2. High-potassium epileptogenesis under altered astrocytes

The extracellular high-potassium theory of epileptogenesis has been supported by a large number of experiments.[21–23] Moreover, increased oscillation amplitude of extracellular potassium concentration is accompanied by

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different epileptic discharge patterns. For example, at higher concentration (8.5 mM) epileptic events with bursting discharge type is maintained,[24] and epileptic activities of "depolarization block" type occur spontaneously with an extracellular potassium concentration close to 40.0 mM.[25] Astrocytes play a key role in regulating the extracellular potassium concentration.[26–28] Astrocytes regulate the level of the extracellular potassium concentration mainly through local uptake by Kir4.1 channels and astrocytic gap junction-mediated spatial buffering.[28–30] Many experimental studies have suggested that the downregulation or dysfunction of local uptake by Kir4.1 channels in astrocytes or the inactivation of astrocytic gap junction protein expression can cause the generation or spread of epileptic activities.[21,22,31,32] Therefore, it is imperative to study the dynamic mechanisms, by which astrocytes regulate the extracellular potassium concentration and the resulting high-potassium epileptogenesis, to further explain the above experiments.

Previous computational models mainly focused on high-potassium epileptogenesis caused by local potassium uptake in astrocytes, and in these models, the simplistic assumptions about the mechanism of potassium regulation by astrocytes were made.[33–35] For example, Kager *et al*. verified that epileptic events would occurr with the extracellular potassium concentration increasing through constructing a neural cable model.[36] Assuming that the sum volume of neuron, extracellular space and astrocyte is a fixed constant, recent mathematic models have presented more diverse mechanisms of ion movement in single neuron,[33,37,38] including sodium and potassium exchange between a single neuron and an astrocyte during the generation of epilepsy.[38,39] Such as, Øyehaug *et al*. constructed potassium and sodium ions' conservation equation and verified that increased extracellular potassium concentration caused by the contraction of extracellular space would active neuron generating spontaneous epilepsy discharges.[40] Cressman *et al*. presented a single neuron-astrocyte coupling model consisting of potassium and sodium ions dynamics, and further revealed that the local uptake by astrocytes is an important factor in inducing epilepsy discharges.[24] More attention has been paid to the high-potassium mechanism induced by altered astrocytes since 2013, and a Kir4.1 channel current model, which depends on the astrocyte membrane potential and extracellular potassium concentration through experimental data fitting, has been proposed.[41,42] Du *et al*. established a model based on astrocyte-neuron network module consisting of a single compartment neuron and 4 surrounding connected astrocytes and extracellular potassium dynamics to further verify the role of high potassium in spontaneous epileptogenesis induced by Kir4.1 channel blockade.[43] In addition, the astrocytic gap junction-mediated potassium spatial buffering is currently studied experimentally. A potassium current model of gap junction channel in astrocytic network has been proposed, and protein deficiencies of gap junctions have been verified to induce extracellular high potassium and resulting epilepsy. The simulation results used by this gap junction-mediated potassium buffering model also yield an interesting conclusion that the epileptic activities gradually generate after a delay of tens of seconds, due to the formation of partially blocked astrocytic gap junctions.[44] The aforementioned studies highlight different methods by which astrocytes regulate the potassium concentration (*e.g*., Kir4.1 and gap junctions),[4] but they all came to the same conclusion that the failure of astrocytes to maintain the proper extracellular potassium micro-environment is critical for initiating epileptogenesis through the high-potassium mechanism.

3. High-glutamate epileptogenesis under altered astrocytes

Extracellular excess glutamate during seizures onset has been observed in many experiments and has inspired researchers to investigate the sources of glutamate during epileptic generation.[45] Carmignoto and Haydon proposed that the excess glutamate underlying epilepsy largely comes from astrocytes through astrocyte calcium oscillations.[45] Astrocyte calcium oscillations have been found to activate the release of glutamate into the extracellular space to bind neuronal NMDA receptors, through which astrocytes play an unpredictable role in epilepsy.[47–49] Although there have been preliminary experimental studies that have shed light on the role of astrocytic glutamate in epilepsy,[50–52] some researchers have questioned the effect of astrocytic glutamate on epilepsy based on the lack of direct experiments.[53–55] However, other scientists have performed direct experiments to support this proposal; they found that astrocyte calcium oscillations are coupled with neuronal seizure activities identically in different astrocyte states, and demonstrated that the persistence of calcium oscillations in astrocytes is sufficient to induce extensive glutamate release, which can induce epilepsy.[56–59]

Computational modelling studies have shed light on the dynamic mechanism of epilepsy under excessive astrocytic glutamate induced by astrocyte calcium oscillations. Initially, Nadkarni *et al*. and other researchers discussed the hyper-excitability of neuronal firings in abnormal astrocytes, and demonstrated astrocytes as excitatory elements for spontaneous and hyper-excitatory abnormal neuronal firings upon mGluR (metabolism glutamate receptors) are overexpression.[60,61] Tang *et al*. found that astrocyte calcium oscillations and neuronal epilepsy discharges promoted each other in neuron-astrocyte coupled network.[61–63] Later, other researchers for example, Amiri *et al*. paid more attention to the NMDA receptors that respond to astrocytic glutamate and found that increased NMDA expression can in-

duce synchronization among population neuronal firings in the hippocampal neuron-astrocyte network, which underlies epilepsy.[16] Recently, Li *et al.*[20] and Flanagan *et al.*[64] utilized different modelling methods to predict epilepsy generated by the abnormal degradation of astrocytic glutamate, which supports the experiments in which epilepsy was found to be correlated with the downregulation of glutamate transporter (GLUT), which is used to transfer excess glutamate to astrocytes.[65] Although these studies revealed the dynamical modulation of astrocytic glutamate in epilepsy in several aspects, the effects of other gliotransmitters such as D-serine, ATP, and GABA on epilepsy remain to be elucidated through experiments on epilepsy.[4,66–69]

4. Epileptogenesis under altered astrocyte voltage-gated calcium channels

The astrocyte resting membrane potential mainly depends on the balance of potassium ions.[70] The accumulation of extracellular potassium induces the astrocyte membrane depolarization caused by the uptake of potassium through the Kir4.1 channels in astrocytic endfeet and then causes the voltage-gated calcium channels (VGCCs) current to flow into astrocytes and increases the level of calcium concentration in astrocytes, thus enhancing the positive feedback effect of astrocytes on neurons as shown in Fig. 1. In addition, an increased intra-astrocyte calcium concentration promotes epoxyeicosatrienoic acids (EETs) production following enhanced calcium levels and BK channel opening by EET in the distal endfeet; this induces the release of potassium ions into the distal space and inhibits astrocyte membrane depolarization, thus ultimately enhancing the negative feedback of astrocytes on neurons caused by a decrease in the VGCCs currents.

Kir4.1 channels and BK channels can prevent hyperexcitability in epilepsy by reducing astrocyte membrane excitability.[71,72] Since VGCCs calcium influx is the main factor that influences the astrocyte calcium concentration,[73,74] the upregulation of astrocyte VGCCs protein expression can increase the level of intracellular calcium.[74–78] Many experiments have found that elevated VGCCs currents in astrocytes increase astrocyte calcium concentration. Note that the enhancement of VGCCs protein expression in astrocytes is closely related to neuronal epileptogenesis.[75] Recent computational studies of epileptogenesis during astrocyte membrane depolarization caused by Kir4.1 channels and BK channels have provided preliminary results. Sibille *et al.*,[41] Witthoft *et al.*,[42] and Harada *et al.*[71] determined a dynamic equation of the astrocyte membrane potential based on Kir4.1 channel and BK channel currents and analysed the astrocyte membrane potential in normal and epileptic state. In addition, Li *et al.*[73] and Zeng *et al.*[79] established the dynamic models of astrocyte VGCCs and found that VGCCs calcium currents are the main source of calcium in astrocytes. Recent computational studies respectively focused on epileptogenesis during depolarization of the astrocyte membrane caused by Kir4.1 and BK channels,[42,71] calcium influx caused by the depolarization of the astrocyte membrane,[79] and the enhancement of the intracellular calcium concentration level caused by calcium release from the astrocytic endoplasmic reticulum after the stimulation of astrocytes with glutamate.[20,60] In fact, these three processes are interdependent. It is urgent to construct a model of the neuron-astrocyte network loop involving potassium and calcium ion metabolism and resulting astrocytic membrane depolarization to study normal and pathological epileptic dynamics.

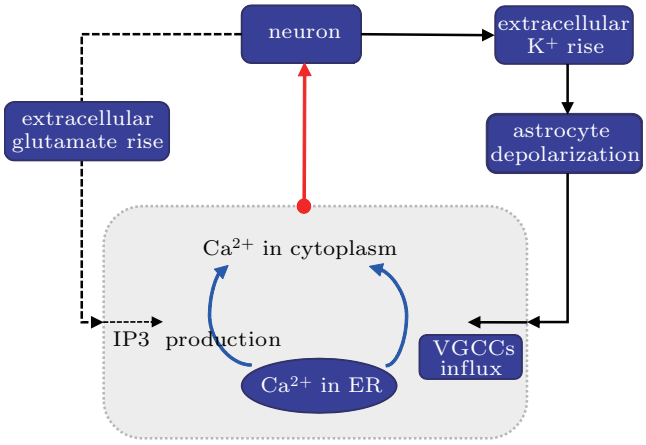

Fig. 1. Sketch of neuron-astrocyte coupled model interacting with calcium and potassium ions.

5. Future: Dynamic mechanism of epilepsy under energy metabolism

Describing the energy expenditure of nervous system from the perspective of a computational model can help to better understand the energy expenditure during epilepsy discharges. Early studies of brain energy show that supported neuronal discharge activity mainly focused on single neuron or neuronal networks by calculating the rate of energy consumption.[27,80–82] Moujahid *et al.* derived an energy consumption formula of the neuron model based on the H–H neural equivalent circuit model.[82] Yu studied the energy efficiency of the cortex neuron.[83] Wang *et al.*[84] and Zheng *et al.*[85] presented a neuron energy calculation method based on the Hamilton theory, the study explained an inexplicable neurophysiological phenomenon that blood flowing into the brain increases dramatically but oxygen consumption increases very little when neurons in the brain are activated. In recent years, as researchers have further understood the role of brain astrocytes in the intermediate bridge by which the capillary supplies energy to neurons, scientists have not only focused on the oxygen consumption of Na^+/K^+-ATPase pumps corresponding to normal and epileptic discharges in the nervous system,[86] but

also determined the dynamic equation of glucose concentration in astrocytes.[87] A large number of astrocytes in the brain through gap junctions wrapped around capillaries,[97] and glucose is absorbed from capillary and converted into lactic acid for energy uptake by neurons as shown in Fig. 2. Many experimental studies have observed that the abnormal degradation and transport of glucose absorbed from capillary by astrocytes are the direct causes of epileptogenesis.[19] Therefore, a dynamic model of a neuron-astrocyte-capillary coupling loop involving energy metabolism can more in depth explain the intrinsic mechanism of energy supply-induced epileptogenesis.

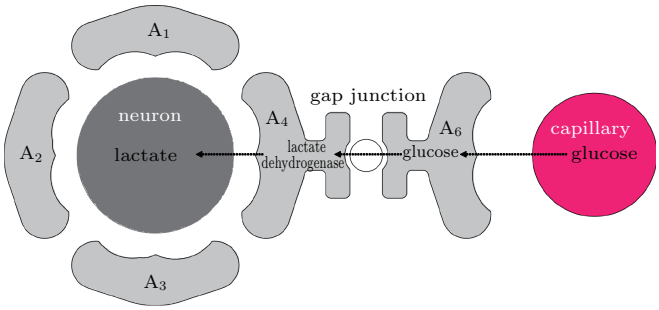

Fig. 2. Schematic diagram of lactate transmission in the neuron–astrocyte–capillary loop. Glucose can be transported through astrocyte capillaries and then transmitted into distant astrocytes by gap junctions. Afterwards, the transmitted glucose is degraded into lactate by lactate dehydrogenase in astrocytes. Finally, this lactate can be absorbed by neurons to sustain action potentials.

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