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Extracellular potassium dynamics in the hyperexcitable state of the neuronal ictal activity

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ABSTRACT

An enduring question in epilepsy research concerns with the mechanisms responsible for the neuronal hyperexcitability. This theme is under debate and different hypotheses have been put forward. One hypothesis relates to extracellular ionic variations, especially the increase of the extracellular potassium concentration ($[K^+]_o$). During the epileptiform bursting, an increase of $[K^+]_o$ is observed which raises the cellular excitability. It remains unclear, however, how the extracellular potassium variation could affect the generation and persistence of epileptiform bursting within the ictal phase, that is, during the epileptic seizure. The neuronal mechanisms responsible for this cellular hyperexcitability are not yet fully understood, hindering the development of more efficient therapies to control epilepsy. Mathematical models with biological plausibility have provided considerable insights into the mechanisms underlying epileptiform pattern. This paper reviews experimental evidences and computational studies concerning effects of the extracellular potassium dynamics on the cellular excitability within the neuronal ictal activity.

1. Introduction

A neuron is an electrically excitable cell. The factors that influence its activity are diverse and depend on the intricate balance of intra and extra cellular ionic concentrations. Patterns of neuronal electrical activity can be altered when there is an abnormal increase in cellular excitability. An excessive electrical activity takes place when the cell is in a state of hyperexcitability – the state of high predisposition for neuronal discharges. This abnormal hyperexcitable behavior is observed in patients with epilepsy. Epilepsy is a common chronic neurological disorder characterized by epileptic seizures. These seizures result from excessive and synchronous discharges in a population of hyperexcitable neurons [1].

We can distinguish two phases in epileptiform activity, the ictal and interictal phases. The ictal term is used to refer to the epileptic seizures. Following the ictal activity, the post-ictal phenomena take place. These phenomena are transient abnormalities of the brain function. Interictal periods are events ranging from the post-ictal phase to the onset of the next ictal one. In the interictal period, the neuronal population has a stereotyped electrical activity called paroxysmal depolarizing shift – PDS. The PDS is characterized by a sudden intensive depolarization of membrane potential that causes a sequence of action potentials – the bursting – lasting for 50–200 ms [2]. In the ictal phase, the membrane potential is abruptly depolarized leading to a bursting of long duration, which lasts for seconds to dozens of seconds [3] (See Fig. 1).

In vitro experiments with slices of hippocampal formation (HF) [8–11] highlighted the role of synaptic mechanisms in paroxysmal epileptiform activity. However, experiments under conditions that cause depression of synaptic transmission,

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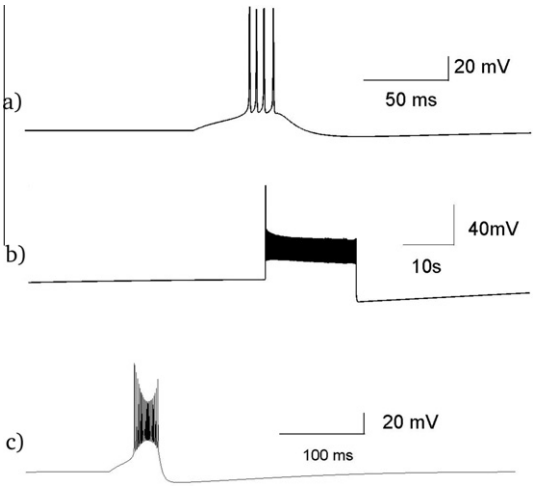

Fig. 1. Burst simulations of somatic, single-compartment models of the hippocampal region CA1. (a) Typical bursting of the hippocampal region CA1, simulation of the mathematical model for zero $[Ca^{2+}]_o$ proposed by Golomb and colleagues [4]. (b) Long-lasting bursting mimicking the neuronal activity in the ictal phase, simulation of the mathematical model for zero $[Ca^{2+}]_o$ and high $[K^+]_o$ proposed by Florence and colleagues [5]. (c) Bursting mimicking the stereotyped electrical activity, the PDS, in the interictal phase, simulation of the mathematical model for normal $[Ca^{2+}]_o$ proposed by Golomb and colleagues [4]. In this case, to generate the PDS, the input stimulation was increased. See experimental recordings concerning these neuronal activity in [4,6,7].

e.g., a low concentration of extracellular calcium, showed that an electrical activity is similar to the patterns observed during seizures [12–14]. These findings reveal the possibility to produce ictal discharges without synaptic transmission. Thus, the non-synaptic mechanisms may play an important role in the epileptiform activity [15].

Ionic fluctuation within extracellular spaces appears as an important non-synaptic mechanism. In particular, the potassium exerts a strong influence in increasing the neuronal excitability. Measurements during the intense ictal discharges revealed an augment in the extracellular concentration of K^+ [16]. Experimental results [17,18] and computer simulations [5,19–21] showed that the increasing averaged concentration of extracellular potassium ($[K^+]_o$) causes extensive changes in neuronal excitability. High $[K^+]_o$ depolarizes cellular membrane and, consequently, may increase the excitability of the tissue to the point of spontaneous neuronal discharges. Such evidences on the extracellular ionic variations highlight the importance of non-synaptic mechanisms at the transition to a hyperexcitable state, typically presented in the ictal activity [22].

Nevertheless, the role of potassium is still controversial, since it is not understood whether the high $[K^+]_o$ is a primary factor in the hyperexcitability or only a secondary factor, as a consequence of excessive neuronal activity [16,23]. Initial studies related to the role of potassium in the epileptiform discharges [24] were oversimplified, mainly due to the limited understanding of the biophysics of neuronal tissue and the lack of efficient computational techniques.

This paper reviews experimental evidences and recent advances in computational modeling concerning possible effects of the extracellular potassium dynamics on the cellular excitability within the neuronal ictal activity. Now a combination of insights coming from a detailed mathematical modeling of the cells, dynamical system theory and elevated computing power provides a suitable framework to further deepening of these studies.

2. Experimental evidences

2.1. Non-synaptic mechanisms underlying the ictal activity

Synaptic responses vanish for values of $[Ca^{2+}]_o$ below 0.2 mM [14]. Studies using ion-selective electrodes during intense neuronal activities reveal a strong reduction of extracellular calcium concentration ($[Ca^{2+}]_o$) [25,26]. Thus, in the course of ictal activity, the synaptic transmissions tend to be depressed. In vitro experiments with slices of HF have shown that certain regions of this structure develop self-sustained epileptiform activities even with the blockade of chemical synaptic transmission [12,14]. These studies indicate that synaptic transmission is not essential to the epileptiform activity.

During the ictal activity, the reduction of extracellular calcium concentration enhances the cellular excitability [6,25–30]. It happens mainly because the decrease of $[Ca^{2+}]_o$ impairs some inhibitory mechanisms of neuronal electrical activity. The low $[Ca^{2+}]_o$ tends to block the inhibitory synapses of interneurons and to depress the effect of hyperpolarizing potassium currents activated by intracellular Ca^{2+}.

An intense neuronal activity causes an increase in the extracellular concentration of potassium [6]. This increase in $[K^+]_o$reduces the potassium driving force.[1] [7] As a consequence, there is a reduction in the intensity of potassium currents.

[1] The drive force is the difference between the membrane and Nernst potentials.

Moreover, there is also evidence for the influence of high $[K^+]_o$ in the depression of inhibitory postsynaptic potentials mediated by $GABA_A$ (gamma aminobutyric acid) [31,32]. The combined effect leads to drastic alterations in the neuronal behavior.

These experimental evidences led some authors to suggest that the transition from interictal activity to ictal one could be induced by changes in the concentrations of $[Ca^{2+}]_o$ and $[K^+]_o$ [33–35].

2.2. Potassium accumulation hypothesis

Frankenhaeuser and Hodgkin [36] observed that K^+ accumulates in the interstitial space during repeated electrical stimulations in the squid giant axon. This accumulation abolishes the hyperpolarization that follows the neuronal activity. Later, Green [37], Fertziger and Ranck [24] suggested that the accumulation of potassium in the extracellular medium, during an intense neuronal activity, could initiate and maintain the epileptic seizures. This hypothesis suggests that the increase in $[K^+]_o$ sets off a regenerative process from which the high $[K^+]_o$ would increase neuronal excitability leading to a bursting behavior. The bursts, in turn, would promote a further growth of $[K^+]_o$ in a process of positive feedback [24].

Some points regarding the influence of $[K^+]_o$ on cell excitability are controversial. Some authors have proposed that the extracellular potassium would not be involved with the onset of seizures [23,38–42]. In this case, the high $[K^+]_o$ would only maintain the high level of excitability during the epileptiform activity. Some arguments contrary to the accumulation of extracellular potassium as a generator of epileptiform activity are: (i) the lack of a single threshold value of $[K^+]_o$ for the onset of seizures, suggesting that potassium would not be a main trigger mechanism of seizures; (ii) large fluctuations in $[K^+]_o$ occur only after the onset of ictal electrical activity. The absence of a prior deep variation in $[K^+]_o$ seems to refute the idea of potassium as a primary factor in the seizure beginning.

The lack of a single threshold value of $[K^+]_o$ for the onset of seizures could be explained by the difficulty of determining it experimentally, since other factors also influence cellular excitability [43]. The wide variation of $[K^+]_o$ after the onset of ictal activity of neurons suggests that this variation is only an effect of intense neuronal activity. Therefore, this observation would indicate that the increase in extracellular K^+ would not be an initiating agent of ictal activity. However, in hippocampal slices, ictal discharges are initiated with a high basal level of $[K^+]_o$ [6].

A number of studies have shown that increased $[K^+]_o$ can act as a primary factor in cell hyperexcitability. Changing the external concentration of K^+ ion by applying a solution containing a high concentration of this ion can generate seizures [44,45]. In tissue slices of the hippocampal formation, solutions with high $[K^+]_o$ induce epileptiform bursts [46–48]. Elevations in $[K^+]_o$ cause the transition from interictal to ictal activity [33–35]. Experiments with solutions containing low $[Ca^{2+}]_o$ demonstrate the role of electrodiffusion of potassium on neuronal tissue on the propagation and synchronization of ictal activity [17,49]. Therefore, these studies have suggested that high $[K^+]_o$ may play an important role in cell hyperexcitability.

3. Computer modelling

3.1. Mathematical models based on cellular mechanisms

The use of mathematical models as a tool for investigating neural mechanisms has expanded considerably in recent decades. Issues that are not accessible experimentally might be better understood with the application of neuronal modeling. Mathematical models based on cellular mechanisms help to understand the neuronal electrical activity in abnormal operating conditions such as the underlying mechanisms of epileptiform activity.

Hodgkin and Huxley were the first to model the generation of action potentials related to the opening and closing of selective ion channels [50]. These authors proposed a model based on a capacitive electrical circuit analogous to the axon membrane functioning as a dielectric of a capacitor. The membrane potential is represented by a differential equation with three ionic currents: a K^+current, a Na^+ current and a leakage current. The conductances of the $K^+$and Na^+ currents are dependent on membrane potential and vary in a nonlinear manner. This model led to important contributions towards the understanding of neuronal signal propagation within the nervous system.

From the early eighties, Roger D. Traub and collaborators produced a series of papers on mathematical modeling of epileptiform activities. These models represent the FH neuronal communications via a model based on an analog circuit. In 1982 these authors presented a model with one hundred neurons of CA2 and CA3 regions (CA: Cornu Ammonis) of FH [9]. In this model, neurons in the network can generate intrinsic bursts and neuronal communication occurs via excitatory chemical synapses. Moreover, other works were also produced [51–53] modeling different types of ionic currents, typically in apical dendrite and soma regions, e.g., transient Na^+ current, high-threshold Ca^{2+} current, delayed rectifier K^+ current, A-type K^+ current, slow Ca^{2+}-activated K^+ current, fast Ca^{2+}-activated K^+ current. Thus, it was possible to reproduce the bursts in the soma and apical dendrites.

Later, several models have been put forward based on the configuration of analog electrical circuit [4,54–61]. In some models, different currents of Na^+ and K^+ were used as the persistent Na^+ current and muscarinic-sensitive K^+ current involved in sustaining and modulation of bursting, respectively [4,60,61].

In general, these works do not pay attention to a wide variety of cellular mechanisms (e.g., extracellular ionic variations, transmembrane ion transport, changes in cell volume, ionic regulation by glia) involved in these neuronal activities and play an important role in alterations of cortical activity, as occurring in the ictal activity. To reproduce these conditions, other

mathematical models have been proposed. The large variations in $[K^+]_o$ during ictal activity and important regulatory mechanisms of potassium were represented in simplified forms [5,19,20,62,63] facilitating the study of the neuronal dynamic behavior and also with a higher level of complexity, allowing a detailed analysis of these mechanisms [21,64]. These papers present studies on paroxysmal activities [19,63], the non-synaptic epileptiform activity [5,20,64], neuronal synchronization [20,65] and the seizure-like after discharges [21], giving important contributions to the understanding of neuronal epileptiform activity.

3.2. The effects of increasing $[K^+]_o$ on the transition to the ictal hyperexcitable state

Certain neurons in the brain exhibit a burst activity, a recurrent transition between fast spikes and a slow rest dynamics. The spiking dynamics consists of the action potentials resulting from the exchange of fast currents such as transient Na^+ current and delayed rectifier K^+ current. These neurons exchange slow currents such as slow Ca^{2+}-activated K^+ current and muscarine-sensitive K^+ current, which may exhibit a slow dynamics: the hyperpolarization. The typical membrane potential of a spiking-bursting neuron consists of bursts of multiple spikes followed by a rest state hyperpolarization [66].

The physiological system is often thought as being the action of two subsystems, a fast and a slow subsystems, linked together. The fast subsystem is responsible for each spike the neuron produces, whereas the slow subsystem is responsible for modulating the intensity of these spikes before eventually triggering quiescence.

The state transitions between bursting and the resting potential have been studied by techniques of nonlinear dynamics [67]. Particularly fruitful studies on the dynamics of bursting are based on bifurcation theory [68–75]. In these studies, the variables that model the ionic currents are divided into two groups that oscillate in different time scales: the "fast" variables, which modulate the action potentials during bursting, and the "slow" variables, which modulate own bursting [75]. Thus, this system can be represented as follows:

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2) \\ \frac{dx_2}{dt} &= \mu f_2(x_1, x_2) \end{aligned} \tag{1.0}$$

The state variable "x_1" denotes the vector of fast variables responsible for the generation of action potentials (e.g., transient Na^+ current and delayed rectifier K^+ current). The vector state variable "x_2" represents the variables that modulate the bursting (e.g., muscarine-sensitive K^+ current and Ca^{2+}-activated K^+ current). The constant "μ" describes the ratio between the time scales of spiking fast modulation and bursting slow modulation. With this separation between fast and slow variables, it is possible to apply the fast-slow analysis [67,74,75]. This method involves an analysis of bifurcation taking the state variable "x_2" as a bifurcation parameter, since "μ" $<<$ 1. This allows the study of modulating effects of certain cellular mechanisms on the dynamics of bursting, like the muscarine-sensitive K^+ current [4], the Ca^{2+}-activated K^+ current [63] and extracellular potassium [5,62].

We can use the fast-slow analysis to study effects of potassium variations on cellular excitability. As $[K^+]_o$ shows a very slow variation, it is possible to treat this variable as a parameter in the bifurcation analysis [62], breaking thus the regulatory

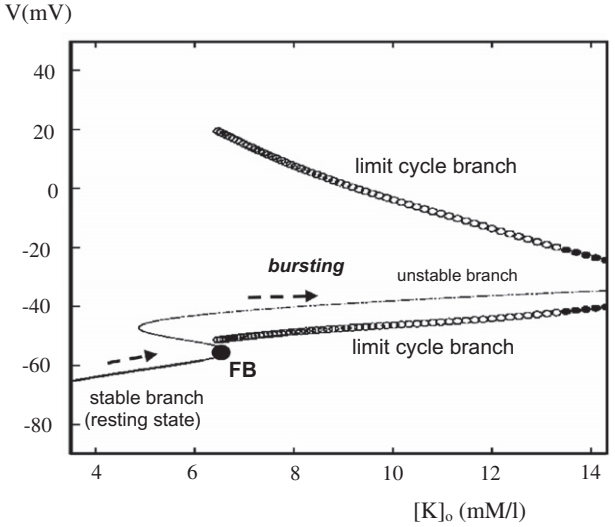

Fig. 2. Bifurcation diagram. The increase of $[K^+]_o$ causes a fold bifurcation (at the point marked FB) when happens the transition from the resting state to the bursting regime (Adapted from [5]).

mechanisms of $[K^+]_o$. This reduction of the full model allows a bifurcation analysis, evaluating the neuron behavior for different levels of $[K^+]_o$ within the limits physiologically plausible.

In Fig. 2, we depict $[K^+]_o$ as a parameter to control the cell excitability. At normal levels of $[K^+]_o$, the cell remains in the resting state, showing no electrical activity. As we increase the $[K^+]_o$, the resting state approaches a bifurcation point, and the resting state becomes unstable. The neuron undergoes a change in its dynamical behavior, exhibiting now an oscillatory regime. This corresponds to the firing threshold, initiating the bursting. This study suggests that increasing the extracellular potassium concentration can raise the level of cell excitability, creating conditions for the generation of epileptiform bursting [5].

The increase $[K^+]_o$ might interfere in different ways in cellular excitability [7]. One of these ways would be through the depression of K^+ currents. This depression is due to the decrease of the potassium driving force. It means that high $[K^+]_o$ leads to the reduction of the driving force, the difference between the membrane potential and the Nernst potential of potassium (see the Eq. (2.0), reducing the intensity of K^+ currents.

$$I_{ioniccurrent} = g_{conductance} * (V_{membranepotential} - E_{Nernstpotential}),$$
$$\text{driving force} : (V_{membranepotential} - E_{Nernstpotential}) \tag{2.0}$$

The K^+ currents are important inhibitory mechanisms of neuronal electrical activity. Thus, the depression of this type of mechanism could create favorable conditions to the transition to the ictal hyperexcitable state.

3.3. Computational studies concerning potassium dynamics

Computational studies of the potassium dynamics suggest their involvement in inducing and sustaining ictal neuronal activity [5]. The primary increase of cellular excitability may occur due to the growth of the basal level of $[K^+]_o$, creating conditions for the generation of ictal activity. Moreover, this process involves high $[K^+]_o$ and cell hyperexcitability continues in the course of the intense neuronal activity. In this case, the hyperexcitability is maintained for a long-lasting bursting through a positive feedback loop between the intense neuronal activity and increased $[K^+]_o$ [76].

The primary raise of cellular excitability induced by high basal level of $[K^+]_o$ can be studied by computer modeling experiments with hippocampal slices bathed in solution with high concentration of K^+ [5]. In this study, the bath solution causes a gradual increase in basal levels of $[K^+]_o$. The increase in $[K^+]_o$ causes a depression of the potassium leakage current. The consequence of this current reduction is an imbalance between the currents responsible for the resting potential of the neuron which produces a positive net result ($I_{net} = \sum I_{(cellular\ currents)} > 0$). Hence, this positive net result causes an initial increase in the membrane potential. During this process, sodium currents are activated, producing a membrane depolarization leading to the bursting eruption. Thus, with elevated $[K^+]_o$, the membrane potential becomes more depolarized, creating the conditions for triggering the bursting.

Computational studies suggest the involvement of potassium in sustaining an intense electrical activity of long duration in epileptic seizures [5,21,77]. Theoretical and experimental studies have demonstrated that short bursts (50–200 ms) typically associated with the interictal phase [2,3] are modulated by K^+ currents in non-synaptic neuronal activities, e.g., muscarinic-sensitive K^+ current at zero $[Ca^{2+}]_{solution}$ [4] and Ca^{2+}-activated K^+ currents in normal $[Ca^{2+}]_{solution}$ [63]. However, in the ictal activity, the modulation of bursts induced by the K^+ currents is impaired. This occurs because there is a reduction in the intensity of these currents due to high $[K^+]_o$, which affects the cell membrane repolarization.

Under these conditions, the membrane potential remains at levels that allow potassium ion channels to remain open during the bursting, continuously releasing the K^+ ion to the extracellular medium. Thus, in a positive feedback process, the continuous growth of $[K^+]_o$ will cause a greater depression in K^+ currents, keeping the state of cellular hyperexcitability. This process of positive feedback contributes to the support of an intense electrical activity of long duration [5].

4. Conclusions

Epileptic seizures occur in abnormal operating conditions of neuronal networks. A neuron alone cannot generate the clinical manifestations of epilepsy. However, the cortical malfunction is commonly associated with some abnormalities of the neuronal functioning [21]. Therefore, to analyze the effects of altered cellular components on the dynamic behavior of neurons is central to the understanding of abnormal oscillatory patterns of the brain.

Issues related to the behavior of cellular mechanisms during ictal activity have been studied by neuronal models. These studies provide insights on how these mechanisms can induce ictal activity. Within this context, discussions about the role of potassium in seizures, initially raised by Green [37], Fertziger and Ranck [24], have recently been taken up and refined in relation to the epileptiform activity [5,19–21,62–65]. The variations in $[K^+]_o$ during ictal activity and regulatory mechanisms of potassium were represented by neuronal models, allowing a detailed analysis of these mechanisms [21,64].

The balance of intra and extra cellular K^+ concentrations is essential to K^+ currents (e.g., K^+ leakage current, delayed rectifier K^+ current, A-type K^+ current, muscarinic-sensitive K^+ current, slow Ca^{2+}-activated K^+ current, fast Ca^{2+}-activated K^+ current, inhibitory postsynaptic current mediated by $GABA_B$). These currents are important inhibitory mechanisms of neuronal electrical activity. Thus, the depression of these mechanisms caused by high $[K^+]_o$ could create favorable conditions to the transition to the ictal hyperexcitable state. Within this context, computational simulations have contributed to

understand possible effects of high $[K^+]_o$ on the dynamic behavior of some K^+ currents. The dynamic analyses of $[K^+]_o$ suggest that high $[K^+]_o$ may play an important role in the onset and sustaining of seizures [5].

Despite the fundamental importance of potassium in the ictal activity, the epileptic seizures are not limited to change to a single mechanism. Other alterations may also create favorable conditions to trigger recurrent seizures, ranging from an imbalance between excitatory and inhibitory synapses, abnormalities in neuronal metabolism in mitochondrial disorders, abnormalities of neuronal structure and organization in cortical malformations to single gene mutations resulting in ion channel malfunctioning [76,78,79]. Therefore, further computational studies involving all these mechanisms are essential to provide a broad understanding of this neurological condition.

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