The impact of the glial spatial buffering on the K^+ Nernst potential

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Abstract Astrocytes play a critical role in CNS metabolism, regulation of volume and ion homeostasis of the interstitial space. Of special relevance is their clearance of K^+ that is released by active neurons into the extracellular space. Mathematical analysis of a modified Nernst equation for the electrochemical equilibrium of neuronal plasma membranes, suggests that K^+ uptake by glial cells is not only relevant during neuronal activity but also has a non-neglectable impact on the basic electrical membrane properties, specifically the resting membrane potential, of neurons and might be clinically valuable as a factor in the genetics and epigenetics of the epilepsy and tuberous sclerosis complex.

Keywords Tripartite synapse · K^+ spatial buffering · Nernst equation · Membrane potential

Introduction

Stable neural processing is dependent on the proper functioning and interaction of the three major compartments of brain tissue: neurons, glia, and extracellular space (ECS). The maintenance of ion gradients across plasma membranes by passive mechanisms, the activity of ionic pumps and transporters is a prerequisite for the establishment of cellular membrane potentials, electrical signalling, and metabolite transport. On the other hand, electrical signalling and synaptic transmission by neurons, are based on,

and result in, ion flow across the plasma membrane, resulting in significant changes in ion concentrations in the extracellular space with modification of ion gradients during neuronal activity (Deitmer and Rose 2010).

The effect of activity-induced ion movements on extra- and intracellular ion concentrations and their electrochemical gradients, respectively, not only depends on the surface-to-volume-ratio of the involved compartments, but also on parameters influencing ion diffusion such as buffering and spatial restrictions due to a complex morphology or a dense extracellular perineuronal net (Syková and Chvátal 1993; Syková 1997; Syková and Nicholson 2008). Of special relevance is the loss of potassium from active neurons, which results in significant increases in the extracellular potassium concentration (Somjen 2002). In their seminal work about 50 years ago, Orkand, Nicholls and Kuffler first suggested that glial cells could act as a spatial buffer for potassium released from active neurons (Kuffler 1967; Kuffler and Nicholls 1966; Orkand et al. 1966). While this concept has been refined and extended, today it is firmly established that glial cells remove excess potassium from the extracellular space by mechanisms like spatial buffering as proposed for astrocytes, or potassium siphoning, proposed in the retina (Kofuji and Connors, 2003; Kofuji and Newman 2009; Newman and Reichenbach 1996). Basically the term “removal” of excess potassium by glial cells stands for the net uptake of potassium at sites of elevated potassium (i.e. where neurons are firing action potentials) and release of potassium at sites where no or little neuronal activity is going on, resulting in a redistribution of extracellular potassium. While there is evidence that glial uptake of potassium is partly mediated by Na^+/K^+ -ATPase, many studies indicate that influx of potassium through inward rectifier ion channels plays a predominant role (Kofuji and Newman 2009).

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The negative resting membrane potential of both neurons and glia cells is not too far from the Nernstian equilibrium for potassium ions (Hodgkin and Katz 1949; Purves et al. 2008; Somjen 2002) and thus, small variations of the potassium concentration in the extracellular space $[K_{ex}^+]$ produces changes in the basic properties of membrane and on the neuronal excitability (Newman, 1985; Somjen 2002). If potassium increases over a so-called ceiling level of about 12 mM, hyperexcitability and epileptiform discharges are induced (Somjen 2002).

Based on these experimental observations, the influence of glial removal of potassium on membrane potentials and firing patterns of active neurons was mathematically modelled from different point of views in earlier studies. In general, these studies followed two main modeling strategies. While one approach focussed on the modeling of local synaptic hyperexcitability and frequency-dependent facilitation of excitatory post-synaptic potentials due to abnormal ionic dynamics with modified Hodgkin-Huxley equations (Clay 2005; Cressman et al. 2009; David et al. 2009; Park and Durand 2006; Somjen et al. 2008), the other strategy investigated the network hyperexcitability phenomena and their impact on epileptogenesis with systems of Hodgkin-Huxley equations and reaction-kinetics models (Ullah et al. 2009).

Although these studies have examined the cellular control of microenvironmental factors as a means to modulate the dynamical neuronal response by modifications of Hodgkin-Huxley equations, little attention has been paid to fundamental electrochemical properties at equilibrium states. Most of these previous models share a common methodology: the models consist of a single-compartment conductance-based neuron containing ions and leak currents, augmented with variables representing the intracellular sodium and extracellular potassium concentrations (Cressman et al. 2009). These concentrations are affected by different influential currents, such as the sigmoidal glial uptake current. Finally, the concentrations are coupled to the membrane voltage equations via the Nernst equation.

However, the fact that the Nernst equation is an equilibrium solution of the Nernst-Planck equation implies that it cannot be represented in a dynamical form. Thus, at equilibrium, it seems to be more appropriate to follow a different strategy to gain an improved understanding of the interactions between the neurons, perisynaptic glia and ECS. Therefore, the Nernst-Planck-Equation is used as the basis framework of the present study to evaluate the influence of glial spatial buffering on neuronal Nernst potentials.

In general, the Nernst-Planck equation

$$\partial_t c(x, t) = \nabla \cdot (-D(\nabla c(x, t) + \gamma c(x, t) \nabla \phi(x, t))) \quad (1)$$

describes the movement of ions in response to a concentration gradient $\nabla c(x, t)$ and an electric field $\nabla \phi$

(x, t) . The parameters D resp. $\gamma = \frac{ze}{kT}$ are in general obtained experimentally and denote the diffusion coefficient of the ion resp. a constant comprised by the ze the electric charge of the ion, k the Boltzmann's constant, and T the absolute temperature. By the simplifying assumption that the field is constant inside the membrane, the Nernst-Planck equation becomes decoupled from the effects of charges moving through the membrane. In this case, the steady state solution of the Nernst-Planck equation provides a relationship between the intra- and extracellular ion concentrations (c_l and c_r resp.) and the potential difference $V = \phi_l - \phi_r$ across the membrane, called the Nernst potential

$$V = \frac{1}{\gamma} \ln \left(\frac{c_r}{c_l} \right). \quad (2)$$

Electrophysiological studies have shown that the Nernst potential appropriately approximates the neuronal membrane potentials (at resting states) for high levels of K_{ex}^+ . At low levels (below 5–6 mM) of extracellular potassium concentrations, the membrane potential is less sensitive to $[K_{ex}^+]$. The rationale of the present study is to mathematically examine, whether this loss of sensitivity is caused by disregarding of the glial influence on $[K_{ex}^+]$ especially through spatial buffering. In addition, the membrane properties at equilibrium (which are fixed for “all time”) point out to genetic aspects of ion channel-related diseases (e.g. epilepsy, and tuberous sclerosis complex), which is of clinical and pre-clinical interest to understand the pathophysiology of those diseases. In conclusion, if the astrocytic spatial buffering has an impact on the equilibrium potentials, then an abnormality in its machinery leads to a permanent pathophysiology such as an increased probability for neuronal hyperexcitability with genetic/epigenetic causes.

For this matter, we first modify the Nernst-Planck equation with a simple but physiologically justified corrector term, denoting the glial feedback to the elevated potassium levels. Subsequently, the impact of this modification on the steady state solutions (Nernst equation) is studied from the analytical point of view. Specific stimulations of the neuronal tissue provide estimations for the level of $[K_{ex}^+]$ removal from ECS via glial spatial buffering. These estimations suggest quantitative ranges for the influence of glia on the neuronal Nernst potentials.

Methods

Poisson-Nernst-Planck equations

The aim of this section is to briefly introduce the concept of the Poisson-Nernst-Planck equations (PNP), which are the

foundation of our mathematical investigation. These equations describe the electrochemical dynamics of ion channels and thus, can be applied to investigate the pathophysiology ion channel-related diseases such as epilepsy, episodic ataxia, malignant hyperthermia, tuberous sclerosis complex, etc.

In order to mathematically formulate the problem, the membrane is idealized as a dielectric layer of thickness $\tilde{l}$ with a cylindrical hole, or channel, of radius p . Inside the channel, we assume that the Nernst-Planck equation (NP) holds. For steady state, this means that the flux J_i of i -ions satisfies the continuity equation

$$\nabla \cdot J_i = 0, \quad (3)$$

which is a three-dimensional formulation. The flux J_i is given by the following constitutive equation:

$$J_i = -D_i(\nabla c_i + \frac{z_i e}{kT} c_i \nabla \phi). \quad (4)$$

Here, D_i is the diffusion coefficient of the i -ions, $z_i e$ their electric charge, k Boltzmann's constant, T the absolute temperature, and ϕ is the electrical potential, which arises partly from the distribution of the ions in the aqueous solution. Indeed, if we assume that the ions on either side of the membrane are uniformly distributed and in neutral electric equilibrium, then the Gauss' law suggests the Poisson's equation

$$\nabla^2 \phi = -\frac{1}{\epsilon} \sum_i z_i e c_i, \quad (5)$$

where ϵ denotes the permittivity¹ of the aqueous solution in the channel region (Barcilon et al. 1992). Because of the major role of K^+ dynamics in establishing the neuronal membrane potentials (at resting state), we will focus subsequently only on PNP respectively NP of this one ion type. In addition, we will consider the one-dimensional NP, which provides the advantage that this drift-diffusion equation can then be integrated analytically (Barcilon et al. 1997) to yield a formula for the concentration of carriers of valence Z for $x \in [l, r]$:

$$c(x) = \frac{1}{\int_l^r e^{Z\phi(y)} dy} \times \left(c_l e^{Z(\phi_l - \phi(x))} \int_x^r e^{Z\phi(y)} dy + c_r e^{Z(\phi_r - \phi(x))} \int_l^x e^{Z\phi(y)} dy \right). \quad (6)$$

¹ A constant of proportionality that relates the electric field in a material to the electric displacement in that material. It characterizes the tendency of the atomic charge in an insulating material to distort in the presence of an electric field.

Statement

As mentioned above, astrocytes remove excess potassium ions at sites where neurons are active, while they release potassium at distant sites (Chen and Nicholson 2000; Kofuji and Newman 2009; Somjen 2002). By affecting the extracellular concentrations of potassium, glia change the coupled system of intra- and extracellular concentrations and thus, alter the overall K^+ concentration. This sensitive response of the astrocytes to variations of the extracellular ion concentrations ∇c (*glial ionic response*) suggests a direct functional relationship:

$$F(c)(x, t) = a - b \nabla c(x, t). \quad (7)$$

The parameter vectors a and b of this affine functional denote the (gradient-independent) glial ionic exchange rate with the ECS, and the glial ion transfer ratio for an ion (dimensionless) times the transfer-velocity, respectively in each space direction. The minus sign on the right hand side of the equation represents the inverse reaction of glia to the concentration gradients, it means if $|a| < |b \nabla c(x, t)|$ (high concentration gradient) then astrocytes starts the ionic

Fig. 1 A schematic representation of the ionic interactions of neurons and astrocytes with the ECS. Parameter a is the glial potassium exchange rate, while spatial buffering is disabled. Parameter b denotes the glial ion transfer ratio for an ion (dimensionless) times the transfer-velocity induced by the K^+ spatial buffering. The gray circles represent the main active ion pumps and co-transporters of the astrocytes: $3Na^+ - 2K^+$ pump, KCC1 ($K^+ - Cl^-$ co-transporter), NKCC1 ($Na^+ - K^+ - 2Cl^-$ co-transporter), and NBC ($Na^+ - HCO_3^-$ co-transporter). The membrane lipid bilayers are assumed to be of the same thickness $\tilde{l}$ for both neurons and astrocytes

clearance, while $|\alpha| > |\beta \nabla c(x, t)|$ forces release of ions into ECS. Figure 1 summarizes the major components of the model statement within the framework of neuron-glia interactions.

The idealized mass conservation law in the synaptic domain suggests to couple the functional of glial ionic response $F(c)$ (as a reaction term) directly with divergence of the flux J_i as an additional drift term:

$$\partial_t c_i = \nabla \cdot J_i + F(c_i). \quad (8)$$

Because of the important role of K^+ in establishing neuronal membrane potentials, the tenuity of potassium channels, and the negligence of the complex dynamical geometry of the membranes and the ECS, it is sufficient to consider the one-dimensional reduction (very narrow ion channels) of the constitutive equation (Eq. 4) for a single ion type with Dirichlet boundary values:

$$\partial_t c = \partial_x (-D(\partial_x c + \gamma c \partial_x \phi)) + F(c), \gamma := \frac{ze}{kT} \quad (9)$$

$\partial_x \equiv \frac{d}{dx}$ denotes the one-dimensional derivative along the x -axis. In this formalism, the glial role as an ionic source and remover depends solely on the gradient of the ion concentrations and not on any external mechanisms. Therefore, it allows us to consider the glial influence on the electrochemical dynamics as an “intrinsic” property of the process. Within this framework, we are able to establish a model of the Nernst-Planck equations with the glial response functional $F(c)$ and to analyze its impact on the behavior of the steady state solutions.

Results

Steady-state solutions

One of the most important equations in electrophysiology is the Nernst equation, which describes how a difference in ionic concentration between two phases can result in a potential difference between the phases. This equation can be derived as a phase space relationship of the steady state solutions of the Nernst-Planck equation. Thus, for $\partial_t c = 0$, the solution of an ordinary differential equation in x (Eq. 10) will provide the relationship between the glial ionic response and the Nernst potentials in the phase space.

Assume $\partial_t c = 0$, explicitly

$$0 = \partial_x (-D(\partial_x c(x) + \gamma c(x) \partial_x \phi(x))) + F(c)(x). \quad (10)$$

If we use the substitution $g(c) := D^{-1} \int F(c) dx$, we then have

$$\partial_x c + \gamma c \partial_x \phi = g(c). \quad (11)$$

Now suppose that the cell membrane extends from $x = 0$ to $x = \tilde{l}$ (the thickness of the membrane) and let subscripts

l and r denote internal and external quantities respectively. Then, integrating from $x = 0$ to $x = \tilde{l}$, leads for $V = \phi_l - \phi_r$ to

$$V = \int_0^{\tilde{l}} \frac{1}{\gamma c} g(c) dx + \frac{1}{\gamma} \ln \left(\frac{c_r}{c_l} \right). \quad (12)$$

The resubstitution of $F(c) = a - b \partial_x c$ in the equation suggests

$$V = \left(\alpha \int_0^{\tilde{l}} c^{-1} dx - \beta \right) + \frac{1}{\gamma} \ln \left(\frac{c_r}{c_l} \right), \quad (13)$$

with $\alpha := \frac{\tilde{l}}{\gamma D} a$ and $\beta := \frac{\tilde{l}}{\gamma D} b$. In other words, the membrane potential at equilibrium is a composition of the Nernst potential $V_N := \frac{1}{\gamma} \ln \left(\frac{c_r}{c_l} \right)$ and the effective perturbation of the membrane potential due to the local ionic alterations induced by glial activity $G(c) := \alpha \int_0^{\tilde{l}} c^{-1} dx - \beta$, which we call the *glial corrector* of the Nernst equation:

$$V = G(c) + V_N. \quad (14)$$

It is obvious that the values of the functional $G(c)$ determines the impact of the glial influence on the equilibrium potentials of the neuronal membranes. Therefore, we will estimate the magnitude of the glial corrector, as an intrinsic characteristic of the system, for very narrow cylindrical potassium channels.

Estimation of $G(c)$ values for one-dimensional potassium channels

As introduced before, the membrane is idealized as a dielectric layer of thickness $\tilde{l}$ with a cylindrical hole, or channel, of radius p . The one-dimensional case ($P = 0$) is considered as the limit of the narrow cylindrical channels with $p \rightarrow 0$. Because the values of the parameters α and β are obtainable from experimental data, it only remains to estimate possible values for the integral $\int_0^{\tilde{l}} c^{-1} dx$, which clearly depends on assumptions about the distribution of ion concentrations inside the channels and on the strength of glial potassium uptake.

In the simplest case of spatial buffering, we can assume that the linearized gradient of K^+ concentration has a positive slope, i.e. $\partial_x c$ is an increasing strict monotone functional on $[0, \tilde{l}]$. This assumption suggests a large class of in general nonlinear differentiable functions representing the potassium concentration. Thus, we are only able to provide an estimation for the most simple case, namely if $\partial_x c = m_1 x + m_2$ with $0 < m_1$, and $0 \leq m_2$. This implies that the ion concentration on the x -axis is of the form

$c(x) = m_1 \frac{x}{2} + m_2 x + c_0$, which leads to the explicit formulation of the glial corrector $G(c)$ as:

$$G(c(x)) = \alpha \left(\frac{2 \tan^{-1} \left(\frac{m_1 x + m_2}{\sqrt{c_0 m_1 - m_2^2}} \right)}{\sqrt{c_0 m_1 - m_2^2}} \right) - \beta, \quad c_0 m_1 \neq m_2^2. \quad (15)$$

Considering the fact that $a = b = 0$ implies the absence of perisynaptic glial ionic response, it appears for the magnitude of the glial response (under the above simplified assumptions for $F(c(x))$), that

$$0 < |G(c(x))|. \quad (16)$$

This inequality, which is the main result of the present study, suggests that there exists a non-vanishing glial influence on the value of neuronal membrane potentials at resting state (classically obtained by Nernst potentials of ions, especially K^+) induced by K^+ spatial buffering mechanism. The exact value and sign of the glial corrector function is strongly dependent on the choice of the parameters. This choice particularly requires physiological hypotheses on the behavior of ions inside narrow channels. In the following, we will provide estimated ranges for the values of $G(c(x))$ based on experimental studies.

First, we estimate the value of the parameter $\beta = \frac{\tilde{l}}{\gamma D} b$. Membranes are typically 4–5 nm in thickness with two regular layers of lipid molecules (a bilayer) containing various types of protein molecules (Kuchel and Ralston 1988). Since ion channels are “holes” across the cell membranes, we identify the length of ion channels with the thickness of the membranes, thus $\tilde{l} \approx 4$ –5 nm. The parameter $\gamma := \frac{ze}{kT}$ for potassium cations in an environment at the normal body temperature $T = 299$ K is easily identified as $\gamma = -697.97$ 1/V. The diffusion coefficient of potassium ions in water has been obtained in experiments (Samson et al. 2003) and is chosen as an estimated values for D in extracellular space: $D = 1.957 \times 10^{-9}$ m²/s. Based on the fact, that the potassium channels such as K_{ir} -channels are very narrow structures (Kofuji et al. 2002; Zhou and Jan 2010), we suppose that the glial ion transfer ratio for potassium $b = \{0, 1\}$ follows the one or nothing principle, i.e. either only one ion can enter the channel at any step or nothing. Within these parameters, the value of the parameter β can be estimated: $\beta \approx -2.9$ to 0 mV.

For the first summand of the $G(c)$ -equation, we still need to provide the values of the parameters a , m_1 , m_2 and c_0 . We identify the parameter m_1 with the strength of glial potassium uptake, which is estimated experimentally (Ballanyi et al. 1987; Cressman et al. 2009) as $m_1 = 66$ mM/s. This values is comparable with experimental studies on impaired K^+ homeostasis (D'Ambrosio et al. 1999;

Djukic et al. 2007; Santhakumar et al. 2003). The parameter c_0 represents the intracellular potassium concentration, hence it is assumed to take the values between 130 and 400 mM (Matthews 1991). The fact that the glial potassium level at $x = 0$ is equal to the intracellular K^+ concentration, implies that it is justifiable to identify m_2 with c_0 without any loss of generality. Unfortunately, there are no experimental estimations for the value of the parameter a , which represents glial ionic exchange rate with the ECS in an equilibrium state for all mechanisms except gradient-dependent ones. Thus, we can only test a range for its hypothetical values between 0 and 500 mM/s. These information suggest that the range of values for the first summand of $G(c)$ is between -0.9 and 0 mV.

The above estimations suggest that the range of the glial impact on the neuronal Nernst potential is approximately between -0.9 and 2.9 mV:

$$-0.9 \text{ mV} \leq G(c(x)) \leq 2.9 \text{ mV}. \quad (17)$$

This means an average glial influence of about +1 mV resp. a current of 100 pA. Although, there are no experimental studies validating these estimations, the calculated electrophysiological values appears to be plausible in the framework of glial research.

Discussion

Impaired extracellular potassium buffering has been proposed as a significant mechanism underlying various neurological deficits related to abnormal neuronal depolarization, hyperexcitability, and seizures (Somjen 2002). Despite the worthwhile computational studies on the influence of glial dynamics on the neuronal membrane potentials (Clay 2005; Cressman et al. 2009; David et al. 2009; Park and Durand 2006; Somjen et al. 2008; Ullah et al. 2009), there exists a need for fundamental investigation of glial influences on synaptic systems at equilibrium states. Potassium and other equilibrium potentials, which are obtained by Nernst equation, are substantial parameters (usually denoted as E_{K^+} and E_{Na^+}) of major electrophysiological equations such as the Hodgkin-Huxley equations. Even small fluctuations in these parameters can lead to long-term hyperexcitability of the membranes causing epileptogenesis. Since they are obtained in equilibrium states, their fluctuations might also be an index for genetic abnormalities.

By modifying the Nernst-Planck equation for ion movement inside cell membranes with a glial response functional (proportional to variations of K^+ concentration gradient), we have shown that there exists a non-vanishing glial influence on the value of neuronal resting potentials (approximated by K^+ Nernstian potential) induced by K^+ spatial buffering mechanism. Our investigation suggests

that the range of the glial impact on the Nernst potential is approximately between -0.9 and 2.9 mV, i.e. an average glial influence of about $+1$ mV resp. a current of 100 pA. While these fluctuations of about 5% of the potassium Nernst potential are comparatively small (as expected), they provide parameter corrections for especially the Hodgkin-Huxley equations (the E_{K^+} parameters), which are essential for further computational investigations of neuron-glia interactions. In addition, the temporal propagation of these fluctuations might also be of interest for studies regarding the stability of neural networks (Kwok et al. 2007; Shi et al. 2008; Jirsa 2008; Liu et al. 2010) and neuronal spiking models (Heinzle et al. 2007). Since these fluctuations are the results of abnormal K^+ spatial buffering in the equilibrium state, they might point out to the clinical relevance of this phenomenon in the genetics and epigenetics of epileptogenesis and tuberous sclerosis complex (Xu et al. 2009), which requires further studies. In a nutshell, our results suggest on the one hand that the value of K^+ Nernstian potential has not been determined accurately until now and should be modified with the glial-induced correction, which consequently suggests the modification of the resting state potassium parameter of the Hodgkin-Huxley equations, and on the other hand a possible genetic role of the spatial buffering mechanism in the pathophysiology of epilepsy and other potassium channel related disorders.

Although the achieved results are feasible from the experimental point of view, the present mathematical model leaves place for improvements. For instance, potassium uptake by glial cells is not only done through channels. There is also evidence that glial cells take up potassium by Na^+/K^+ -ATPase or other transporters such as $Na^+/K^+/2Cl^-$ -co-transport. Because these processes are mainly governed by the gradient of ion concentrations, the subsequent modifications of the Nernst-Planck equation by these processes appear to be of the same form as the introduced functional $F(c) \approx \nabla c$. Therefore, it is expected that the extension of our model with further gradient-dependent uptake mechanisms reveal a similar analytical behavior with a potentially different range for the values of the glial impact. Nevertheless, the consideration of different types of ions in the modeling of glial homeostatic processes will increase the complexity of the mathematical analysis and requires further investigations.

However, the plausibility of these results in the framework of glial research provides a perspective for future experiments and a revision of the classical concept of the biophysical modeling of the neuronal Nernst potentials as a pure neuronal process by considering the non-neglectable glial homeostatic influence.

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