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Article

Competitive bidirectional pathways of vascular tone regulation via arachidonic acid metabolites

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Abstract. ***Background and Objectives*:** The processes taking place in each element of a neurogliovascular unit will have repercussions in the entire unit. Astrocytes produce arachidonic acid, and its metabolites play a key role in neurogliovascular dynamics with a possibility for bidirectional control, specifically *EETs* and PGE_2 have a vasodilatory effect while *20-HETE* acts as a vasoconstrictor. We develop a minimalistic model of model of neurogliovascular unit which takes into account the effect of arachidonic acid metabolites on the blood vessel radius, determining the blood flow and further activity of the elements. ***Materials and Methods*:** In order to test the model, we simulate two scenarios of model behavior, including an external influence leading to an increase in neuronal potassium, and an external influence on *EETs*. ***Results*:** We have proposed a mathematical model of the neurogliovascular unit, which accounts for IP_3-dependent calcium dynamics in the astrocyte, neuronal activity, and vascular dynamics, and relies on arachidonic acid and its metabolites as vasoactive substances. Numerical simulations have demonstrated the plausibility of such a control loop involving the elements of the neurogliovascular unit and associated with the influence of arachidonic acid metabolites on vascular tone and indirectly on synaptic activity. We conclude that the model can be used for further theoretical studies of the regulatory mechanisms pertaining to cerebral perfusion.
Keywords: astrocyte, arachidonic acid, synaptic activity, neurogliovascular unit

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Конкурентные двунаправленные пути регуляции тонуса сосудов воздействием метаболитов арахидоновой кислоты

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Аннотация. ***Предпосылки и цели***: Процессы, происходящие в каждом элементе нейроглиоваскулярной единицы, будут иметь последствия для всей структурной единицы. Астроциты продуцируют арахидоновую кислоту, и её метаболиты играют ключевую роль в нейроглиоваскулярной динамике благодаря возможности двунаправленного контроля, в частности *EETs* и PGE_2 оказывают сосудорасширяющее действие, а *20-HETE* действует как вазоконстриктор. Для учёта влияние метаболитов арахидоновой кислоты на радиус кровеносных сосудов разработана минималистическая модель нейроглиоваскулярной единицы, определяющая кровоток и активность элементов. ***Материалы и методы:*** Для проверки модели используются два сценария ее поведения, включая внешнее воздействие, приводя-

щее к увеличению нейронального калия, и внешнее воздействие на *EETs*. ***Результаты:*** Предложена новая математическая модель нейроглиоваскулярной единицы, включающая в себя уравнения, описывающие IP_3-зависимую кальциевую динамику в астроците, нейронную активность, васкулярную динамику с учётом синтеза арахидоновой кислоты и её производных. Проведена численная проверка работоспособности модели, показавшая, что она успешно воспроизводит известные пути регуляции активности элементов нейроглиоваскулярной единицы, связанные с влиянием метаболитов арахидоновой кислоты на тонус сосудов и опосредованно на синаптическую активность. Модель может быть использована для дальнейших теоретических исследований функционирования нервной ткани головного мозга и, в частности, механизмов перфузии.

Ключевые слова: астроциты, арахидоновая кислота, синаптическая активность, нейроглиоваскулярная единица

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Introduction

Depolarization waves in the cerebral cortex are accompanied by a large number of ion flows: in addition to the release of potassium ions by neurons into the intercellular space and the inwards current of sodium ions, excess potassium ions in extracellular medium are absorbed by astrocytes and blood vessels, in large amounts [1]. Thus, both neurons and astrocytes are important in maintaining the homeostasis of the cerebral cortex tissue.

The neuronal pathway for increasing the activity of the nervous tissue leads to the rapid formation of nitric oxide (*NO*) in neurons by the *NO* synthase. It causes dilation of blood vessels, which facilitates the increase in oxygen supply, thus allowing for sustained activity. The astrocytic pathway is associated with changes in the level of calcium in astrocytes, leading to the synthesis of arachidonic acid (*AA*) derivatives that promote dilation (*EETs*, PGE_2) or constriction (*20-HETE*) of blood vessels [2]. The net direction of the vasomotor effect linked to cortical spreading depolarization (CSD) wave is determined by oxygen concentration in brain tissue, while the astrocytic role in this process depends on its own metabolic and activation state, which in turn can be noticed by subcellular changes in calcium concentration, but the precise mechanism remains unclear [3].

The synthesis of *AA* derivatives on its own is also determined by the oxygen concentration in nervous tissue. Under hyperoxic conditions, an increase in the level of calcium in astrocytes leads to the release of vasoactive metabolites of *AA* from their endfeet into blood vessels and subsequent vasoconstriction; normoxic and hypoxic conditions are accompanied by vasodilation [4]. An increase in glial calcium and subsequent formation of *AA* derivatives also affects the activity of neighboring synapses [5].

Astrocytes are activated and play a protective role after ischemic stress caused by the propagation of CSD wave [6]. This, together with high plasticity, makes these cells a suitable object for modulation of neuron activity during pathological processes by regulating astrocytic calcium dynamics, which under certain conditions, allows neurons to return to normal functioning.

Recently, a number of models have been proposed that describe neuronal activity, calcium waves in astrocytes, the interaction of neurons and astrocytes, and neurovascular coupling with varying degrees of detail (see, for example, reviews [7–9]).

There is a clear tendency to combine all three components into an integrated complex construction, which started with the introduction of the concept of a neurovascular unit (NVU), which includes the neuron, the astrocyte, the intercellular space surrounding them, and the nearby blood vessel. The concept of NVU took a long time to firmly establish itself in the scientific community and was more or less directly referred to in many papers. Though, interactions in distinct parts of NVU are mentioned much earlier, for example, in the research of neuronal activity modulation and arterioles dilatation propagation in the cerebellum cortex [10]. The final concept of NVU was formulated as the result of the Progress Review Group meeting of the National Institute of Neurological Disorders and Stroke of the NIH [11]. Further neuronal dynamic studies in the brain revealed the necessity to also include the dynamics of glial cells-astrocytes into the model (for example, [12]). Some of the models of interaction of its elements are given in the theoretical review [8]. Most of them do not consider the role of *AA* metabolites synthesized in astrocytes in regulatory processes, being limited exclusively to modeling calcium waves in astrocytes and neuronal activity. Models that do consider the effect of *AA* derivatives are limited to including only individual metabolites, without giving a full picture of the interactions.

For example, the model of the neurogliovascular unit (NGVU) (combination of a neuron, astrocyte and blood vessel), considered in [13], reproduces the dynamics of potassium and *NO* in neurons, the glutamate-determined calcium dynamics in astrocytes, as well as *EETs*-mediated signaling to blood vessels, but does not take into account other key *AA* metabolites, that affect blood flow (*20-HETE*, PGE_2). The model [14] also considers exclusively the effect of *EETs* and does not take into account the mechanism associated with nitric oxide, due to the lack of experimental results on its effect at that time. Another main mediator between neuronal activity and vascular dynamics is PGE_2 introduced in the NGVU model presented in [15]. In contrast to previous models, *EETs* are not taken into account here. In addition, all these models neglect the role of oxygen supply to the nervous tissue, as such, they do not take into account the different scenarios of the behavior of the entire system during hypoxia and hyperoxia.

At the same time, experimental data [16] indicate the key role of *AA* derivatives and *NO* in the control of blood flow and neuronal activity, including critical situations accompanied by hypoxia or hyperoxia. This means that understanding of such processes is impossible without creating a new complex mathematical model that covers all processes of synthesis of *AA* metabolites and *NO* and their functional interactions.

Another limitation of the existing modeling studies of neuronal dynamics and CSD wave is their emphasis on the leading edge, while the trailing edge is the crucial point for external control of the synaptic activity, which determines the degree of neurological deficit and the return speed of the nervous tissue to the normal state. For practical application, a complex NGVU model, which is both quite realistic from a biophysical point of view and simple in terms of computation, is a good starting point for developing methods for controlling blood flow and brain activity during pathological processes.

In this work we develop a mathematical model of NGVU components, described by dynamic equations for neuronal activity, astrocytic calcium dynamics and vascular activity, with *AA* metabolites as additional variables. To discuss the obtained numerical results we use known experimental findings associated with *AA* metabolites.

Model

For a theoretical study of the effect of *AA* and its derivatives on the functioning of the nervous tissue, we propose a simple local mathematical model of NGVU. Based on the experimental data, we show the main regulatory dependencies associated with the elements of NGVU as the functional diagram, which is presented in Fig. 1.

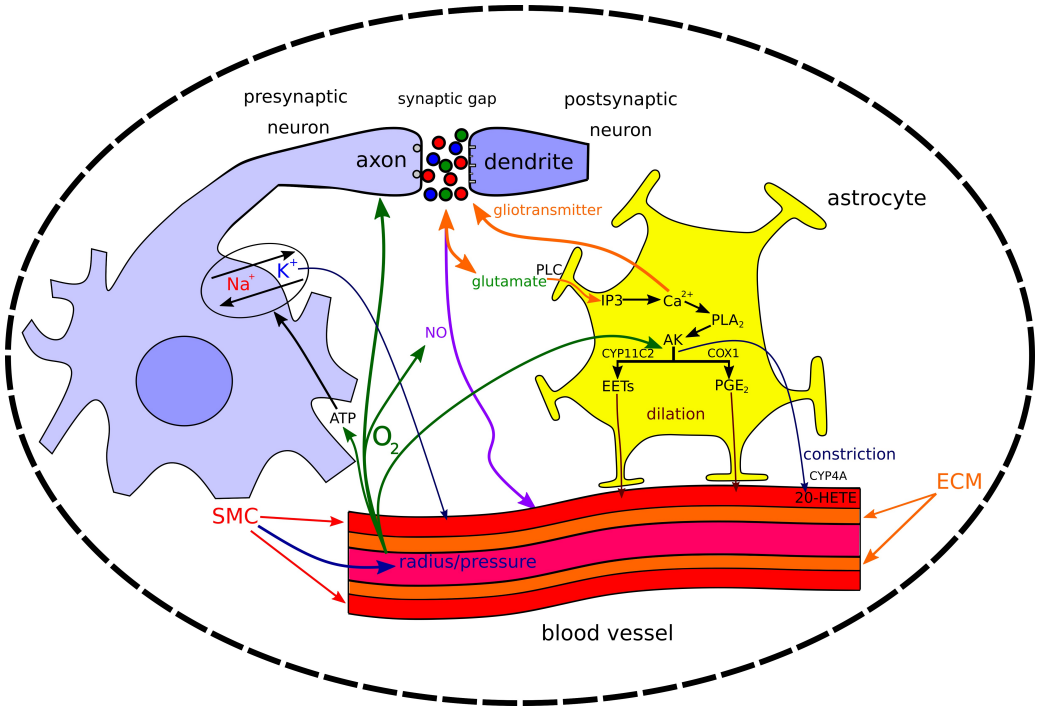

Fig. 1. Model of a neurovascular unit (color online)

Astrocyte

To model calcium dynamics in an astrocyte, we use the IP_3-dependent calcium dynamics Ullah model [17], which was extended by including the surface-to-volume ratio (SVR) parameter, which allows to take into account the morphological features of the astrocyte cell [18]. The model includes the following variables: concentrations of cytoplasmic calcium $[Ca^{2+}]_c$, endoplasmic reticulum calcium $[Ca^{2+}]_{ER}$, inositol triphosphate$[IP_3]$, and gate variable h for the variable $[IP_3]$:

$$\frac{d[Ca^{2+}]_c}{dt} = (1-SVR)J_{ER} + SVR(J_{in} - J_{out}); \quad (1)$$

$$\frac{d[IP_3]}{dt} = SVR(J_\delta + J_{Glu}) - \frac{[IP_3]-[IP_3]_0}{\tau_r}; \quad (2)$$

$$\frac{d[Ca^{2+}]_{ER}}{dt} = (1-SVR)J_{ER}; \quad (3)$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}. \quad (4)$$

A detailed description of the currents included in the equations can be found in the original works [17, 18]. Here we emphasize that the connection of the astrocyte with neurons in the model is described by current J_{Glu} accounting for the effect of glutamate on the production of IP_3: $J_{Glu} = v_{Glu} MM([Glu]^{0.3}, k_{Glu}^{0.3})$. Here and below, to describe the Michaelis–Menten dynamics, we introduce the function

$$MM(x,y) = x(x+y)^{-1}. \quad (5)$$

We add the equation for arachidonic acid $[AA]$ production:

$$\begin{gathered}\frac{d[AA]}{dt} = \frac{[AA]_0 - [AA]}{\tau_{AA}} + \\ + k_{AA} \cdot MM([Ca^{2+}]_c^2, k_{mAA}^2) - \\ - k_{AA,buf}[AA] - \\ - (k_{EETs} \cdot MM([AA]^2, k_{mEETs}^2) + \\ + k_{PGE_2} \cdot MM([AA]^2, k_{mPGE_2}^2)) \cdot MM(PO_2^2, k_{mPO_2}^2).\end{gathered} \quad (6)$$

To model the dynamics of [AA], we take into account (see Fig. 1) that an increase in the calcium level in astrocytes stimulates the release of *AA*, which, on the one hand, is released from the astrocytes endfeet into the extracellular space and blood vessels, leading to a further increase in the level of 20-HETE [4] (see (10)–(11)), and on the other hand, is used for oxygen-dependent synthesis of *AA* derivatives [19]. Therefore, the rate of $[AA]$ production depends on $[Ca^{2+}]_c$ concentration, and the flow rate is related to the formation of vasodilatatory metabolites, such as *EETs* and PGE_2. The last term in the equation describes the leakage of $[AA]$ from the astrocyte into the extracellular space and then into the smooth muscle of the circulatory system. The value of $[AA]$, as well as the partial pressure of oxygen PO_2 determine the production of vasodilatatory metabolites [19], the equations for $[EETs]$ and $[PGE_2]$ have the following forms (the last terms in the equations describe the external influence on the system):

$$\begin{gathered}\frac{d[EETs]}{dt} = \frac{[EETs]_0 - [EETs]}{\tau_{EETs}} + \\ + k_{EETs} \cdot MM([AA]^2, k_{mEETs}^2) \times \\ \times MM(PO_2^2, k_{mPO_2}^2) + f_{EETs},\end{gathered} \quad (7)$$

$$\begin{gathered}\frac{d[PGE_2]}{dt} = \frac{[PGE_2]_0 - [PGE_2]}{\tau_{PGE_2}} + \\ + k_{PGE_2} \cdot MM([AA]^2, k_{mPGE_2}^2) \times \\ \times MM(PO_2^2, k_{mPO_2}^2) + f_{PGE_2}.\end{gathered} \quad (8)$$

Circulatory system

To describe the radius r of the circulatory system, we use the equation

$$\begin{gathered}\frac{dr}{dt} = \frac{r_0 - r}{\tau_r} + k_{r,NO}[NO] + \\ + k_{r,EETs}([EETs] - [EETs]_0) + \\ + k_{r,PGE2}([PGE_2] - [PGE_2]_0) - \\ - k_{r,HETE}([HETE] - [HETE]_0).\end{gathered} \quad (9)$$

We account that NO activates soluble guanylyl cyclase (sGC) – physiologic receptor for NO – and causes vasodilation [20]. We also include the vasodilatory effect of *EETs* and PGE_2, as well as vasoconstricting effect of *20-HETE* [4]. To simplify our model we suppose that the velocity of the vascular radius change is linearly proportional to the deviation of metabolites from their respective stable concentrations. The respective coefficients were chosen by hand, so that the response of vascular radius to the changes in variables, would be in biophysical range. The last one designates the concentration of *20-HETE* governed by the equation

$$\begin{gathered}\frac{d[HETE]}{dt} = \frac{[HETE]_0 - [HETE]}{\tau_{HETE}} + \\ + k_{HETE} \cdot MM([AA]_{ext}^2, k_{mHETE}^2) \times \\ \times MM(PO_2^2, k_{m_{ext}PO_2}^2) + f_{HETE},\end{gathered} \quad (10)$$

with the production rate determined by PO_2 and $[AA]_{ext}$ in smooth muscles. Here the leakage of arachidonic acid from the astrocyte into the smooth muscle

is described by the equation

$$\frac{d[AA]_{ext}}{dt} = k_{AA,buf}[AA] - k_{HETE} \times \\ \times MM([AA]^2_{ext}, k^2_{mHETE}) \cdot MM(PO_2^2, k^2_{m_{ext}PO_2}). \quad (11)$$

Intercellular space

The connection between the elements of NGVU is described by variables responsible for the partial pressure of oxygen PO_2, which depends on the radius of the blood vessel and decreases due to oxygen consumption by the brain ($CMRO_2$), the concentration of nitric oxide $[NO]$, the value of which depends on PO_2, as well as the release of glutamate $[Glu]$, determined by the concentration of potassium $[K]_o$, increasing as a result of neuronal activity:

$$\frac{dPO_2}{dt} = \frac{PO_2^0 - PO_2}{\tau_{PO_2}} + k_{PO_2,r}(r_0 - r) - CMRO_2 \cdot PO_2; \quad (12)$$

$$\frac{d[NO]}{dt} = \frac{[NO]_0 - [NO]}{\tau_{NO}} + k_{NO} \cdot MM(PO_2^2, k^2_{mNO}); \quad (13)$$

$$\frac{d[Glu]}{dt} = \frac{[Glu]_0 - [Glu]}{\tau_{Glu}} + k_K \bar{v}([K]_o). \quad (14)$$

NO plays an important regulatory role in the functioning of NGVU components and depends on a large number of endo- and exogenous factors [21], but to minimize the complexity of the proposed model, we restrict ourselves to the representation of neuronal nitric oxide synthase depending on the value of partial pressure of oxygen [22], while NO is formed by the oxidation of nitrogen. For the model simplicity we represent that the simulated effects in our model have a linear character and are MM-dependent, being aware of the fact that such a representation is a lot simplified. In this case, the normalized value of PO_2 is determined by the deviation of the vessel radius from its normal value, and the activation of glutamate occurs during the formation of neuronal activity.

Neuron

The model constructed in the work already contains a large number of variables. To fully describe the functioning of NGVU, we include a block responsible for describing neural activity. Modeling using the classical Hodgkin–Huxley formalism is numerically too complicated and redundant to achieve the goals set in the article. In this regard we use the minimalistic neuron model proposed in [23], considering the stimulation of the potassium membrane potential as a process that reflects the intensity of neuronal excitation. According to [23], we describe neuronal activity in terms of variables $[K]_o$ and $[Na]_i$, which are the concentrations of intercellular potassium and sodium, respectively,

$$\frac{d[K]_o}{dt} = \frac{[K]_{bath} - [K]_o}{\tau_K} - \\ -2\gamma I_{\text{pump}} + \delta_K \bar{v}([K]_o) + \\ + k_{K,PO_2} \cdot MM((PO_2 - PO_2^0)^2, k^2_{mK,PO_2}) + f_K, \quad (15)$$

$$\frac{d[Na]_i}{dt} = \frac{[Na]_i^0 - [Na]_i}{\tau_{Na}} - 3I_{\text{pump}} + \delta_{Na} \bar{v}([K]_o), \quad (16)$$

where the Na^+/K^+ pump current is taken from [24] in the form

$$I_{pump} = \frac{\rho k_{Kpump} \cdot MM(PO_2^2, k^2_{mPump})}{(1 + \exp(3.5 - [K]_o))(1 + \exp((25 - [Na]_i)/3))}, \quad (17)$$

while the firing rate of an excitatory population is described as

$$\bar{v}([K]_o) = \begin{cases} 0, \text{ if} [K]_o < 4.5; \text{ otherwise} \\ -63.9093 + 20.0921[K]_o - \\ -1.53505([K]_o)^2 + \\ +0.0533615([K]_o)^3 - \\ -0.000690027([K]_o)^4. \end{cases} \quad (18)$$

Equations (15)–(18) are a minimal and sufficient set to adequately describe neuron activity without drastically increasing computational complexity. In doing so, we include in the equation for potassium the dependence on the deviation of PO_2 from the normal value, based on the experimental data from [25].

Results

In the numerical simulation we use the set of parameters associated with IP_3-dependent calcium dynamics in the astrocyte described in the previous work [18]. The values of the parameters for other elements of NGVU and their connections are given in Table 1. The modeling parameters were chosen in a way to reproduce the known *in vivo* dynamics of model variables.

In order to test the model, we simulate two scenarios of model behavior: an external influence leading to an increase in neuronal potassium (Fig. 2, *a*), and an external influence on *EETs* (Fig. 2, *b*). In Fig. 2, *a* we stimulate the neural element of the system by means of an external influence in the time interval 400–550 seconds with potassium at a rate of $[K]_{ext} = 0.03 mM \cdot s^{-1}$. As a result, there are oscillations in potassium and sodium. In this case, when the value 4.5 is exceeded by $[K]_o$, the firing rate function $\bar{v}([K]_o)$ is activated, and $[Glu]$ burst

Table 1. Model parameters

$[AA]_0$	0.1 μM	τ_{AA}	0.1 s	k_{AA}	0.1 μM/s	k_{mAA}	0.3 μM
$[HETE]_0$	0.001 μM	τ_{HETE}	0.1 s	k_{HETE}	0.3 μM/s	k_{mHETE}	0.1 μM
$[EETs]_0$	0.035 μM	τ_{EETs}	0.1 s	k_{EETs}	1.95 μM/s	k_{mEETs}	0.01 μM
$[PGE_2]_0$	0.01 μM	τ_{PGE_2}	0.1 s	k_{PGE_2}	0.01 μM/s	k_{mPGE_2}	0.01 μM
$[Glu]_0$	0 μM	τ_{Glu}	0.1 s	k_K	0.1 μM	$CMRO_2$	0.6 s^{-1}
$[NO]_0$	0 μM	τ_{NO}	0.02 s	k_{NO}	8 μM/s	k_{mNO}	1 a.u.
PO_2^0	1.0 a.u.	τ_{PO_2}	0.05 s	k_{mPO_2}	0.3 a.u.	k_{mK,PO_2}	1.4 a.u.
r_0	0.1 mm	τ_r	0.5 s	$k_{m_{ext}PO_2}$	0.01 μM	k_{mPump}	1.4 a.u.
$[K]_{bath}$	3.0 mM	τ_K	100 s	k_{K,PO_2}	15 mM/s	$k_{PO_2,r}$	12 $mm^{-1}s^{-1}$
$[Na]_i^0$	10 mM	τ_{Na}	20 s	$k_{r,HETE}$	100 s^{-1}	k_{Kpump}	3 a.u.
SVR	0.6 a.u.	f_{EETs}	0; 0.25 μM/s	$k_{r,EETs}$	3.55 s^{-1}	$k_{AA,buf}$	0.1 s^{-1}
γ	10 a.u.	f_{HETE}	0; 0.02 μM/s	$k_{r,PGE2}$	0.1 s^{-1}	δ_K	0.02 mM
ρ	0.2 mM/s	f_K	0; 0.03 mM/s	$k_{r,NO}$	0.25 s^{-1}	δ_{Na}	0.03 mM

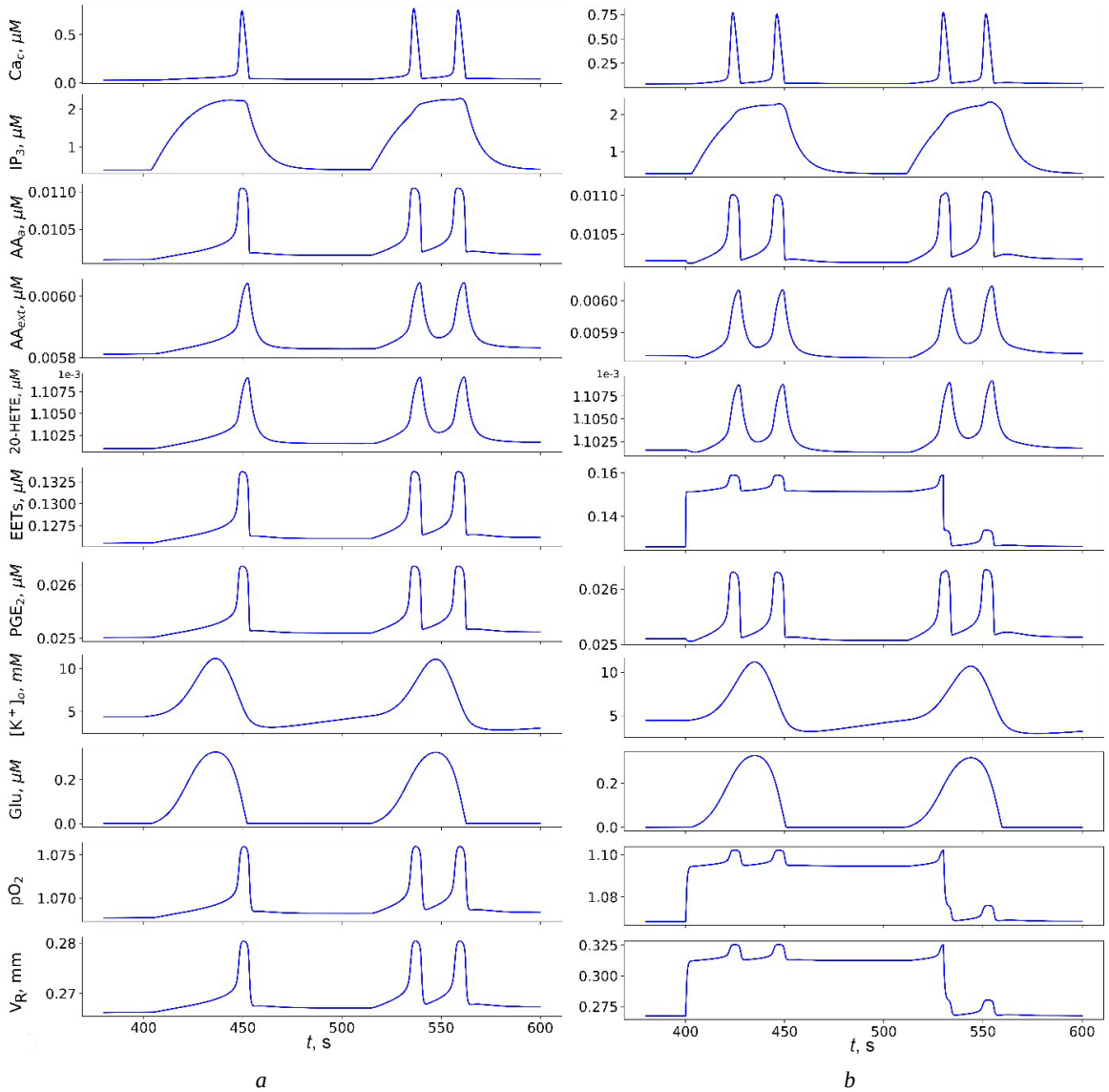

Fig. 2. Results of the numerical solution of the model: (*a*) potassium dynamics in neurons leads to the synthesis of *AA* metabolites; (*b*) an increase in the $[EETs]$ level leads to the amplification of neuronal and calcium astrocytic dynamics

occurs. In turn, glutamate triggers IP_3-dependent calcium dynamics: it leads to the appearance of a flow J_{Glu} that increases the value of astrocytic $[IP_3]$ and further occurrence of $[Ca_c]$ oscillations. An increase in $[Ca_c]$ leads to the synthesis of $[AA]$ and its derivatives $[EETs]$ and $[PGE_2]$ and $[AA]$ leakage into the intercellular space and growth with the formation of $[HETE]$. Due to the impact of metabolites on the blood vessel, its radius r and partial pressure of oxygen PO_2 increase, stimulating the K^+ pump current. This loop results in oscillations in NGVU shown in Fig. 2, *a*.

The numerical solution of the model shows that NGVU activity can also be increased by external stimulation by vasodilating metabolites of *AA*. In Fig. 2, *b* we create an external pulse $f_{EETs} = 0.25$ μM·s^{-1} of the *EETs* metabolite over a time span of 400–550 s. As a result, there is a dilation of the vessel leading to an increase in the partial pressure of oxygen which turns on the K^+ pump current, triggering further activation of the firing rate function, release of $[Glu]$ and emergence of IP_3-dependent calcium oscillations, which finally leads to an oscillatory regime occurrence. After the end of the external influence of *EETs*, we see the last biforked peak and then the system stabilizes.

Depending on the type of influence of *AA* metabolites on vascular tone, it is possible not only to increase the activity of the NGVU, but also to damp oscillatory dynamics. So, Fig. 3 shows the solution of the model, in which, starting from 400 seconds, a continuous external stimulation of the system with potassium was performed at a rate of $[K]_{ext} = 0.03$ μM·s^{-1}. However, starting at 800 seconds, the metabolite *20-HETE* is added to the system at an external pulse intensity of $f_{HETE} = 0.02$ μM·s^{-1}. As a result, we have vasoconstriction and disappearing of any activity.

Discussion

The proposed model includes the main processes occurring within and between the elements of NGVU. At the present stage of neuroscience development, a sufficient amount of data has been accumulated confirming that there is a “reverse” effect of the vasomotor activity rhythms on the excitation patterns of neurons. This fact allows us to consider vessels as a full-fledged component of the brain computing center, which contribute to information processing as well as neurons and astrocytes, while most models of cerebral circulation describe neurovascular interactions exclusively in the neuron → vessel direction. Currently, there is no complete model that takes into account all the key mechanisms of blood flow control during the CSD wave.

Based on recent experimental studies, we supplement the model with processes associated with

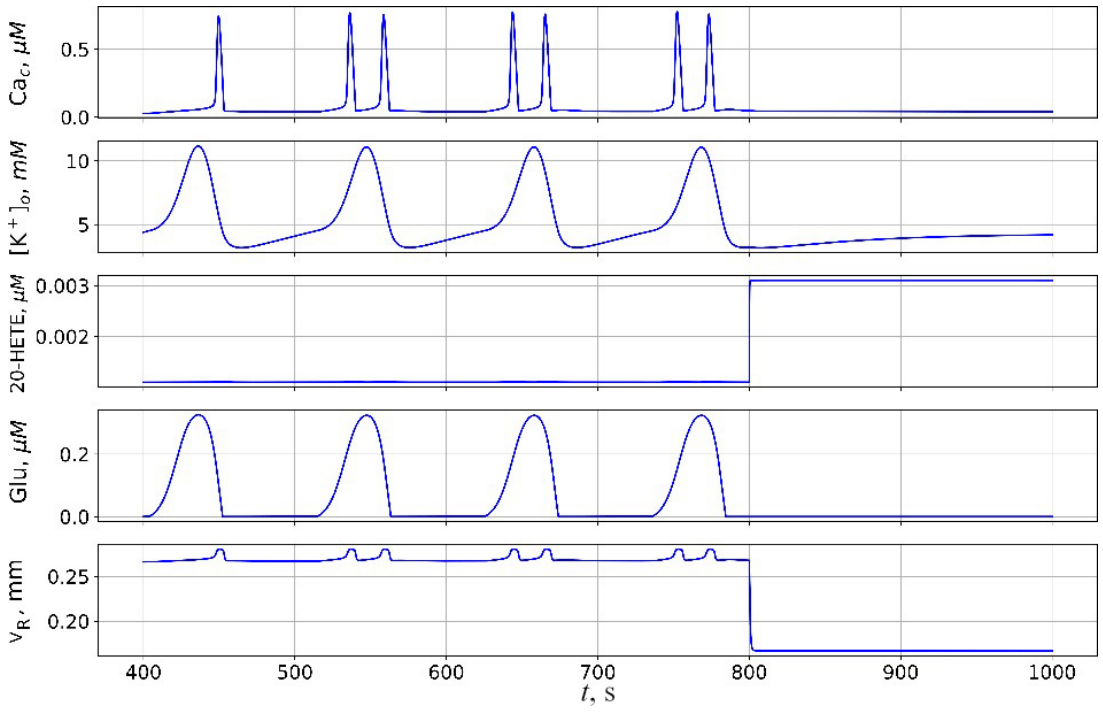

Fig. 3. Results of the numerical solution of the model: External stimulation by *20-HETE* leads to the suppression of neuronal and astrocytic calcium activity

the synthesis of *AA* in the astrocyte and further synthesis of acid derivatives directly in the astrocyte and smooth muscle layer of the blood vessel. The proposed model takes into account the effect of *AA* metabolites on the blood vessel radius, determining the blood flow and further activity of the elements of NGVU. To avoid excessive complexity, we neglect various potential regulatory mechanisms in modeling (in particular, the effect of neuromodulators on NGVU activity, background activity of *NO* synthase, calcium transients in astrocyte endfeet), and describe several processes with a sufficient degree of simplification (for example, we model the effect of PGE_2 on vessels as a direct one, since it has not yet been established whether PGE_2 promotes vasodilation by acting on astrocytes or directly on smooth muscle cells; we consider a minimalistic model of neuronal activity through potassium dynamics, thereby not including depolarization mechanisms of vascular smooth muscle under sufficiently high potassium levels). Nevertheless, the proposed model made it possible for the first time to reproduce the complex interactions of neurons, astrocytes, and blood vessels, taking into account the significant contribution made by the dynamics of *AA* and its metabolites. Despite a large number of simplifications, the model successfully simulates the experimentally observed processes associated with the effect of astrocytic calcium dynamics on the formation of *AA* and further on the activity of neurons through vasomodulatory roles of *AA* metabolites [26], the dependence of *AA* synthesis on oxygen concentration in the nervous tissue [19], the bidirectional (constriction/dilation) regulation of vascular tone by *AA* metabolites [4], including the competitive roles of vasomodulators PGE_2/*EETs* and *20-HETE*, an increase in the level of which can be used to reduce blood flow and inhibit increased activity [2].

In the future, it is planned to extend the model to a spatial case that takes into account the spatial morphology of an astrocyte in order to study the features of the formation of spatially propagating waves and pathways to control them. The first step in this direction is represented in Figs. 2, 3 which can promote the search for selective pathways to control the activity of the elements of NGVU associated with the external stimulation by *AA* metabolites, the combined action of which can regulate vascular tone by dilation or constriction of the blood vessel. It is assumed that the proposed model has good prospects for understanding the pathways of regulation of blood flow and neuronal activity, which can be used, among other things, to develop new therapeutic approaches to reduce the degenerative consequences of ischemic brain damage that occurs in stroke, Alzheimer's disease, and various traumatic brain injuries.

The model proposed in the work made it possible to describe a number of essential processes that determine the activity of the nervous tissue, and can serve not only as an appropriate tool for the theoretical study of processes in the nervous tissue, but also as a basis for a model study of ways to manipulate the balance of blood flow supply and neuronal activity through stimulation of the synthesis of *AA* metabolites.

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