Computational simulation: astrocyte-induced depolarization of neighboring neurons mediates synchronous UP states in a neural network

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Abstract Although recent reports have suggested that synchronous neuronal UP states are mediated by astrocytic activity, the mechanism responsible for this remains unknown. Astrocytic glutamate release synchronously depolarizes adjacent neurons, while synaptic transmissions are blocked. The purpose of this study was to confirm that astrocytic depolarization, propagated through synaptic connections, can lead to synchronous neuronal UP states. We applied astrocytic currents to local neurons in a neural network consisting of model cortical neurons. Our results show that astrocytic depolarization may generate synchronous UP states for hundreds of milliseconds in neurons even if they do not directly receive glutamate release from the activated astrocyte.

Keywords Astrocyte · Synchronous UP state · Slow inward current · Release of glutamic acid · Neural network model · Adaptive exponential integrate-and-fire model

1 Introduction

Though information processing in the brain is generally regarded as the work of neurons, the role of glia has attracted attention in recent years. Previously, glia were thought to serve only a simple auxiliary role. Neurons respond to electrical stimuli by generating action potentials, whereas glial cells exhibit no electrical activity even when an external

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electrical stimulus is applied. However, following the development of techniques for measuring intracellular calcium concentrations, it is now possible to observe responsive changes in calcium concentration inside glia [1]. Since then, various glial activities have been reported [2, 3].

Glia can be broadly classified into three subtypes: astrocytes, oligodendrocytes and microglia. Astrocytes are located adjacent to neurons and are involved in a broad range of functions including synaptic plasticity, neuronal excitability and regulation of the strength of synaptic transmission through the release of glutamic acid, D-serine and adenosine triphosphate [4–9]. An elevation in astrocytic calcium concentration has been reported to actively reduce concentration of extracellular potassium ions, which has an impact on neuronal activity [10, 11]. The fact that neurons and astrocytes respond synchronously to sensory stimuli, for example stimulation of whiskers in the barrel cortex of mice, also implicates astrocytes in the processing of sensory information [12].

Astrocytes release glutamic acid by means of an elevation in intracellular calcium; glutamic acid then binds to the extrasynaptic N-methyl-D-aspartate (NMDA) receptors of neighboring neurons, resulting in the depolarization of these cells [13, 14]. In the CA1 of the hippocampus, astrocytes have been reported to trigger the synchronous depolarization of multiple neighboring neurons through the release of glutamic acid [15]. This experiment was performed under conditions where synaptic interactions between neurons were inhibited, so depolarization occurred in cells within 100 μm of the neurons, which approximates the physical distance between neurons and astrocytes. In actual neural circuitry, astrocytic glutamic acid release not only impacts neighboring neurons but may modulate synaptic interactions between neurons, influencing synchronous activity in the neural network [14, 16, 17]. Such astrocyte-dependent neuronal depolarization has been confirmed to occur in the hippocampus, thalamus and cortex [14, 18, 19]. It has also been reported that astrocytic calcium concentrations rise with various stimuli, such as electrical stimuli or shared agonists of glutamatergic and purinergic receptors, thus triggering depolarization of adjacent neurons [14, 20, 21].

In cortical slices, where there are interactions between neurons via synaptic connections, it has been shown that the depolarization that accompanies persistent firing activity, and is caused by elevated astrocytic calcium, occurs synchronously in multiple neurons. It occurs at a distance of approximately 400–600 μm from the original cell [22]. The UP state is a stable state attractor in neural networks and is believed to be involved in working memory [23] and in the synchronous activity of distant brain sites like the cortex and hippocampus [24]. In many instances, astrocytic glutamic acid release causes a synchronous depolarizing current in neurons located within 100 μm ; it may not be assumed that synchronous UP states in cells within 400–600 μm are the direct result of this release [14].

Astrocyte-induced depolarization of neighboring neurons has been shown to be mediated primarily by glutamic acid acting on extrasynaptic neuronal NMDA receptors [14]. However, if α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are inhibited, the synchronous UP state is inhibited and there is no effect on astrocytic intracellular calcium levels to provoke release of glutamic acid [22]. Inhibiting AMPA receptors inhibits the synaptic interactions between neurons that are dependent on AMPA receptors. This consequently suggests that synaptic interactions between neurons are necessary for the initiation of synchronous UP states. However, there is no direct evidence that astrocytic glutamic acid release is involved in neuronal depolarization and the development of synchronous UP states.

Therefore, this study will use a mathematical model of astrocytes and neural networks to show that UP states are synchronously triggered in neurons due to the propagation, via

synaptic connections, of the effects of synchronous depolarization and firing of multiple adjacent neurons caused by the astrocytic release of glutamic acid.

Recently, it has been reported that the astrocyte-neuron communication is bidirectional: endocannabinoids released by action potentials increase astrocytic calcium levels through type 1 cannabinoid receptors (CB1) [25] and then astrocytes release glutamate that modulates the excitability and synaptic transmission through activation of NMDA [25, 26] and metabotropic glutamate receptors (mGluR1) [27]. For example, endocannabinoid and mGluR1 mediated synaptic potentiation is known [27]. In this study, however, we focus on the effects of the single pathway from an astrocyte to neurons and the role of this pathway in modulating astrocyte-neuron communication. This is because we attempt to answer the fundamental question of whether an astrocyte can trigger UP states by itself even without the endocannabinoid-mediated feedback from neurons to the astrocyte.

2 Methods

In order to examine how an astrocyte in a neural network may influence the synchronous depolarization of multiple adjacent neurons, we constructed a mathematical model that allowed us to insert depolarizing currents, caused by the release of glutamic acid by an astrocyte, into a neural network. Figure 1 shows the schematic structure of our mathematical model. We employed a neural network model [28] with synaptic connections from Brette and Gerstner's adaptive exponential integrate-and-fire (aEIF) model [29]. One feature of this model is its ability to reproduce representative neuronal behavior in the cerebral cortex by merely adjusting the parameters. The computer simulation was carried out using a mathematical model coupling 12,000 nerve cells, at a probability of 2%, unless otherwise indicated. Section 2.1 provides a more detailed description of the model. However, because the details of the mechanism by which astrocytic glutamic acid release causes neuronal depolarization are unknown, stimulation of 1–10 nerve cells within the network was realized using a mathematical model [30] that reproduces changes in depolarizing currents observed

Fig. 1 Schematic structure of our model composed of an astrocyte and neurons. The neural network consists of pyramidal cells (triangles) with excitatory synaptic projections and interneurons (circles) creating inhibitory synaptic connections (filled synapses); cells were randomly coupled. An astrocyte (decagon) depolarizes neighboring pyramidal cells via glutamic acid

in neurons adjacent to astrocytes when astrocytes are stimulated in physiological experiments. Section 2.2 describes the model of nerve cell depolarization by astrocytes. In the present study, we used the Runge-Kutta method, with a 0.1 ms incremental width for time in the numerical calculation of ordinary differential equations. The model was programmed using C++ in Visual Studio Express 2013 for the Windows Desktop environment.

2.1 Network model

We used the following model [28], an extension of an aEIF model [29], as our neural network:

$$C_m \frac{dV_i}{dt} = -g_L(V_i - E_i^L) + g_L \Delta_i \exp\left(\frac{V_i - V_T}{\Delta_i}\right) - \frac{(w_i - I)}{S} - \sum_j g_{ji}(V_i - E_j), \quad (1)$$

$$\frac{dw_i}{dt} = \frac{1}{\tau_w}(a(V - E_i^L) - w_i). \quad (2)$$

Here, V_i is the membrane potential of the i th neuron, $C_m = 1 \mu\text{F}/\text{cm}^2$ is the membrane capacitance, $g_L = 0.05 \text{ mS}/\text{cm}^2$ is the leak conductance, $\Delta_i = 2.5 \text{ mV}$ is the rate of change of the exponential term, $V_T = -55 \text{ mV}$ is the threshold value for firing, $S = 20000 \mu\text{m}^2$ is the surface area of the cell, g_{ji} is the synaptic conductance from a neuron j to i and w_i is the adaptation variable of neuron i . I is the input current, where $I = I_{SIC}$ when there exists a depolarizing current input from the astrocyte, otherwise $I = 0$. The reversal potential $E_j = 0 \text{ mV}$ if the synaptic connection from neuron j to neuron i is excitatory and $E_j = -80 \text{ mV}$ if it is inhibitory. The value of E_i^L was determined in accordance with the normal distribution $N(-70.7, 0.6^2)$ so as to represent the resting membrane potential value of $-70.7 \pm 0.6 \text{ mV}$ from physiological experiments [22]. Firing occurs when the membrane potential V_i exceeds $V_T = -55 \text{ mV}$; the membrane potential is fixed to V_{reset} for 2.5 ms as an absolute refractory period once the membrane potential V_i exceeds 20 mV. For the adaptation variable w_i (nA), the dynamics vary depending on parameter a (μS) and time constant τ_w (ms); b (nA) is added if the membrane potential exceeds 20 mV.

Changing the parameters a , b , V_{reset} and τ_w gives the aEIF model the ability to reproduce behaviors of the membrane potential seen in the cerebral cortex, such as burst firing and adaptation. This numerical experiment used excitatory regular spiking (RS), intrinsically bursting (IB) and inhibitory fast spiking (FS) cells [28, 29, 31]. RS neurons were set at: $a = 0.001 \mu\text{S}$, $b = 0.005 \text{ nA}$, $V_{reset} = -60 \text{ mV}$ and $\tau_w = 600 \text{ ms}$. IB neurons were set at: $a = 0.001 \mu\text{S}$, $b = 0.04 \text{ nA}$, $V_{reset} = V_T + 5 \text{ (mV)}$ and $\tau_w = 144 \text{ ms}$. FS neurons were set at: $a = 0.001 \mu\text{S}$, $b = 0 \text{ nA}$, $V_{reset} = -60 \text{ mV}$ and $\tau_w = 600 \text{ ms}$. The initial membrane potential value for all nerve cells was $V_i = -73 \text{ mV}$.

If parameter b , added to w_i during firing, was greater than 0, then it was possible to generate adaptation, where the firing rate gradually reduced, though the same intensity of stimulation current continued to be applied. The aEIF model is a neuronal model that includes exponential terms, modifying the two-variable nerve cell model proposed by Izhikevich. The aEIF model yields membrane potential behaviors that are close to the Hodgkin and Huxley model, which considers several types of ion channel and reduces computational costs similarly to the Izhikevich model [29, 31, 32]. The first term in (1) brings the membrane potential V_i closer to the resting membrane potential E_i^L . The second term in (1) includes the exponential function, which rapidly increases and spikes when the membrane potential V_i exceeds the firing threshold value V_T . The third term in (1) indicates the adaptation variable and external stimulus.

The synaptic conductance between cells is either excitatory (g_{ji}^E) or inhibitory (g_{ji}^I). In response to presynaptic neuronal firing, g_{ji}^E and g_{ji}^I are incremented by g_e and g_i , respectively. They also conform to the following differential equations, respectively:

$$\frac{dg_{ji}^E}{dt} = -\frac{1}{\tau_{we}} g_{ji}^E, \quad (3)$$

$$\frac{dg_{ji}^I}{dt} = -\frac{1}{\tau_{wi}} g_{ji}^I, \quad (4)$$

where $\tau_{we} = 5.0$ ms and $\tau_{wi} = 10$ ms are time constants of excitatory and inhibitory conductance, respectively.

To adjust to a biologically valid synaptic conductance value, we first studied the magnitude of change in membrane potentials in postsynaptic cells caused by a single spike (the excitatory postsynaptic potential, EPSP). Figure 2a shows the EPSPs of postsynaptic cells in response to presynaptic cell firing under conditions where two RS cells were prepared and an excitatory synaptic coupling was established between presynaptic and postsynaptic cells. Firing of the presynaptic cell at $t = 200$ ms caused the excitatory synaptic conductance to increase by an increment of g_e and the membrane potential of the postsynaptic cell rose in accordance with (1). Attenuation of the excitatory conductance, in accordance with (3), returned the membrane potential to the resting membrane potential E_i^L . The amplitude of the EPSP from the resting membrane potential (-70.7 mV) increased in proportion to the value of the synaptic conductance g_e (Fig. 2b). In the present study, this influence was relatively small, as, for the sake of simplicity, the number of neurons was set to a value smaller than the actual number of neurons. To compensate for this, we set the value of the added excitatory synaptic conductance to $g_e = 2.8$ nS, in order to generate an EPSP of approximately 3 mV, which is somewhat higher than the 1–2 mV EPSPs usually observed. In turn, the magnitude of the inhibitory synaptic conductance value was set at $g_i = 31.3$ nS, in order to keep a $g_e : g_i$ ratio of 6 : 67, which is similar to the ratio of the excitatory to inhibitory synaptic conductance values used by Destexhe [28].

An actual brain is composed of a very large number of neurons; in mice, 100,000 neurons are found in just 1 mm^2 of cortical surface [33]. The present study describes a neural network

Fig. 2 Excitatory postsynaptic potentials (EPSPs) in response to an input spike. **(a)** Representative EPSPs generated in a postsynaptic neuron, with a resting membrane potential of -70.7 mV, by a single spike. The graph depicts EPSPs under changing synaptic conductance values: $g_e = 6$ nS (solid line), $g_e = 3$ nS (broken line) and $g_e = 0.45$ nS (dotted line). **(b)** Magnitude of EPSPs generated in a postsynaptic cell from a single spike when the synaptic conductance g_e was changed

model consisting of 12,000 nerve cells. Given the ratio of cortical surface to cell counts in previous experiments [22] measuring astrocyte-dependent UP states in mouse neocortical slices, this number of neurons corresponds to a 300–400 μm square of cortical surface. In other words, we set our cell count to 12,000 as this number was of a similar order of magnitude to the length of the diagonal of a $300 \times 400 \mu\text{m}$ rectangle and the distance between 400–600 μm neuronal pairs observed in a synchronous UP state and at which a minimal computational cost could be reached. Also, because the release of glutamic acid by astrocytes has been reported to directly and synchronously stimulate neurons within 100 μm [14], we assumed glutamic acid would be released to a region composed of < 1,000 neurons (one twelfth of this region).

We also assumed that any pair of neurons in the 12,000 neurons would couple at a probability of 2%. Neurons were configured so that 20% of neurons would be inhibitory FS cells and the proportions of excitatory RS and IB cells would be 48% and 32%, respectively, in accordance with experimental data from cortical slices [34]. Each cell was numbered: 1–5760 were RS cells; 5761–9600 were IB cells; and 9601–12000 were FS cells.

2.2 Modeling depolarizing current induced by an astrocyte

As the details of the mechanism by which glutamic acid release from astrocytes causes neuronal depolarization are unknown, a mathematical model [30] for reproducing depolarization currents, based on data from *in vivo* stimulation of astrocytes, was used to induce a depolarization current to one, or several, neurons in the neural network:

$$\tau_{dec} \frac{dI_{SIC}}{dt} = -I_{SIC} + m_A S(t), \quad (5)$$

$$\frac{dS}{dt} = -\frac{S}{\tau_s} + m_s \delta(t - t_{SIC}). \quad (6)$$

I_{SIC} is the depolarizing slow inward current (SIC) in a neuron, S is the stimulus current that triggers the depolarizing current and δ is the delta function of magnitude 10 with time width 0.1 ms. To obtain a depolarizing current of similar and sufficient magnitude to cause neurons to fire in physiological experiments [35], the parameters were time constant of depolarizing current $\tau_{dec} = 75$ ms, magnitude of depolarizing current $m_A = 20$, time constant of stimulus current $\tau_s = 100$ ms and magnitude of stimulus current $m_s = 40$.

From the onset of the depolarizing current ($t = t_{SIC}$), the value of S increases in a delta function to generate the depolarization current SIC. Figure 3a shows the time variation in the depolarization current (I_{SIC}) when $t_{SIC} = 0$. The mean depolarizing current induced by an astrocyte is approximately 100–150 pA but depolarizing currents in the order of 500 pA have been observed; in some instances, burst firing of neurons was also triggered [14, 18, 35]. Thus, though it is greater than the mean, we cannot assume that the maximum depolarizing current of 337 pA shown in Fig. 3a would be too large.

Figure 3b shows the membrane potential following application of the depolarizing current from an astrocyte to a RS model neuron. The neuron sustains its firing for approximately 200 ms after the RS neuron starts to fire. The membrane potential remains higher than the resting potential until approximately 500 ms after the onset of the stimulus. In other words, the impact of the depolarizing current from the astrocyte on a neuron is approximately five times as long as the duration of the EPSP (Figs. 2 and 3). Figure 3c shows the membrane potential when the depolarizing current is applied to an IB cell. The IB neuron fires at a higher frequency than the RS neuron in response to the depolarizing current from the astrocyte; however, the firing duration is shorter.

Fig. 3 Effects of depolarizing slow inward current (SIC) induced by an astrocyte. **(a)** SIC generated in a neuron by astrocytic release of glutamic acid. **(b)** Changes in membrane potential when SIC is applied to an excitatory regular spiking (RS) cell. The membrane potential begins to rise at the onset of the depolarizing current ($t = 0$ ms), following sustained firing activity for approximately 200 ms. **(c)** Changes in membrane potentials when SIC is applied to an intrinsically bursting (IB) cell. Though the IB cell fires at a higher frequency than the RS cell, its firing duration is shorter

3 Computer simulations

Application of a depolarizing current by an astrocyte to 10 neurons in a 12,000 cell neural network resulted in the generation of a state of depolarization (an UP state), accompanied by sustained firing for several hundred milliseconds. On the other hand, only when a large number of RS cells were fired synchronously in the neural network, the persistent UP state was not detected.

3.1 Action potentials evoked by an astrocyte

Physiological experiments have reported that depolarizing astrocytic currents occur simultaneously in about 10 neurons [14]. Thus, in this computer simulation, a depolarizing astrocytic current was applied to six RS cells (nos. 1–6) and four IB cells (nos. 5,761–5,764) from time $t = 100$ ms ($t_{SIC} = 100$ ms). As a result, firing occurred even in neurons that were not directly induced to fire by the astrocytic stimulus current. Figure 4 is a typical example of a raster plot of neuronal firing; overall, neuronal burst-firing lasted for approximately 600 ms. This duration is within the range of duration of spontaneous activity of 0.5–3 s (mean 1.5 ± 0.1 s) reported in a physiological experiment using small *in vivo* cortical slabs (where synaptic connections with other sites were severed in a $10 \text{ mm} \times 6 \text{ mm}$ slice of cortical surface) [34].

Assuming that the duration of an UP state is defined by the period from when the mean membrane potential of pyramidal neurons firstly exceeds the mean resting potential (-70.7 mV) and to the time when it decreases below -70.7 mV, the average duration of an UP state was 683.7 ms and the SD was 545.5 ms ($n = 100$). The distribution of the durations is shown and discussed in Section 3.3. In the case of Fig. 4, an UP state starts at $t = 106.5$ ms and ends at $t = 787.4$ ms, therefore the duration is 680.9 ms. As noted in the previous section, the duration of firing for one cell following astrocytic stimulus was approximately 100–200 ms (Fig. 3b,c), whereas the firing duration of neurons was longer, approximately 600 ms (Fig. 4). This is thought to be due to not only the direct depolarizing astrocytic current but also the recursive synaptic coupling between neurons. If only one neuron was depolarized following a depolarizing astrocytic current, there was no continuous firing activity and only the neuron to which the depolarizing current was applied fired. Likewise, if the additional synaptic conductance value was reduced to $g_e = 0.9$ nS ($g_i = 10.05$

Fig. 4 Raster plot of neuronal firing following depolarizing astrocytic current. Initially, six excitatory regular spiking (RS) cells and four intrinsically bursting (IB) cells fired after application of a depolarizing astrocytic current at time $t_{SIC} = 100$ ms. Of the 9,600 excitatory pyramidal cells, cells 1–5,760 are RS cells, 5,761–9,600 are IB cells and 9,601–12,000 are inhibitory fast spiking cells. The boundaries between RS, IB and inhibitory cells are shown by dotted lines

nS), at which nearly 1 mV EPSP is generated, then only neurons to which the depolarizing current was applied fired and a sustained UP state did not occur.

3.2 Synchronous UP states in neurons

Under the experimental conditions described in Section 3.1, the membrane potentials of many pyramidal cells were in UP states during the firing activity caused by astrocyte stimulation. Fig. 5 shows a typical example of changes in membrane potentials in (a) a RS cell and (b) an IB cell, which are from the same simulation trial as Fig. 4 in simulation results by various random seeds (changes in synaptic connections). Each line segment in the graphs represents the mean membrane potential over $t = 180.0\text{--}787.3$ ms and the dotted line represents the firing threshold ($V_T = -55$). During this period, the mean RS cell membrane potential was -61.43 mV and the mean IB cell membrane potential was -61.37 mV, where both are depolarized at midway between the resting membrane potential and threshold value. The changes in membrane potentials shown in Fig. 5 are very similar to those observed in actual cortical slices [22, 34]. For example, neuronal activity during UP states was sometimes accompanied by firing and other times not; this was not because the membrane potential was always elevated but because, in some instances, it fell to near the resting membrane potential. Some IB cells did, in turn, show burst firing. Burst firing has also been observed in UP states in actual cortical small slabs [34]. During the firing period induced by astrocytic stimulus, many cells fired but there were also cells that did not fire at all.

Figure 6 shows the mean membrane potentials for all pyramidal cells in this simulation trial. During firing activity, pyramidal membrane potentials, as a whole, were in a higher state than resting membrane potentials. If the cells that did not fire are excluded from the calculation of this mean, the mean value increases. Meanwhile, the ensemble mean value of the adaptation variable w_i increased with time, from the onset of astrocytic stimulus, reaching its peak and then decreasing after a while (Fig. 7). This suggests that adaptation of

Fig. 5 Example of synchronous UP states following astrocytic stimuli. Changes in membrane potentials in (a) a regular spiking (RS) cell (pyramidal cell no. 4803) and (b) an intrinsically bursting (IB) cell (pyramidal cell no. 6567). Line segments show mean membrane potentials over a firing activity of 180.0–787.3 ms duration and dotted lines show firing threshold membrane potentials ($V_T = -55$ mV). Mean membrane potentials were (a) -61.43 mV and (b) -61.37 mV

each neuron acts on the network as a whole, by which the mean firing rate decreases and a wide-ranging UP state may be terminated synchronously.

As the number of neurons impacted by the astrocytic stimulation decreases, UP states occur less readily. Using a neural network of 2,000 cells, a coupling probability of 2% and synaptic conductance values of $g_e = 6$ nS, $g_i = 67$ nS, the number of neurons depolarized by astrocyte-derived stimulus varied between 1–10. Depolarization of 6 or more neurons resulted in nearly 100% UP states, 5 resulted in 75%, 4 in 65%, 3 in 30% and when < 2

Fig. 6 Mean membrane potential averaged over all pyramidal neurons. We assume the duration when this value is higher than the resting membrane potential indicates an UP state. The line segment shows the mean membrane potential averaged over the 180.0–787.3 ms duration (-66.25 mV) and the dotted line shows the firing threshold membrane potential ($V_T = -55$ mV)

Fig. 7 The ensemble mean value of the adaptation variable

neurons depolarized, UP states essentially no longer occurred. Thus, the probability of UP states decreased rapidly when the number of depolarized cells decreased to a few.

3.3 Comparison with effects of synchronous neuronal stimuli

Could the synchronous UP state described above also occur following direct neuronal stimulation, or is it a unique property of astrocyte stimulation? We induced direct synchronous firing into some RS cells to examine whether this would also result in a sustained UP state in the overall network or not. We used the same model described in Section 3.1. In this experiment, 192 cells (nos. 1–192), corresponding to 2 % of the total pyramidal cells, were synchronously fired at $t = 60$ ms. Firing was initiated by programming the membrane potentials to be greater than the threshold. As shown in Fig. 3b and c, if 1 astrocytic stimulus was received, then RS cells fired 9 times and IB cells fired 10 times. In Section 3.1, astrocytic currents (SIC) were directly applied to 6 RS cells and 4 IB cells, for a total of 94 spikes ($9 \times 6 + 10 \times 4$) to be applied to the network. Here, 2% of the pyramidal cells ($9600 \times 0.02 = 192$), which implies more than twice the 94 spikes, were initially applied. Despite the large number of provided spikes, the mean period of UP state was 322.4 ms ($n = 50$). Figure 8 shows the raster plots of a representative case, in which the UP state duration was 43.5 ms ($t = 60.1$ – 103.6 ms). Actually, the durations of UP state are distributed for both cases, through SIC ($SD=545.5$ ms) and direct neuronal stimuli ($SD=463.5$ ms), because sustained reverberated signals can be generated by recurrent connections stochastically settled in the neural network. Figure 9 shows the stacked histogram of durations of UP state for both two cases. In Fig. 9, the amount of frequency in each case is 100%, respectively. Without the stimulus from an astrocyte, 64% of the durations were less than 100 ms; such as a case is shown in Fig. 8. On the other hand, when activated through SIC of an astrocyte, the duration becomes obviously longer (mean 683.7 ms), with a range of 108.3–2522.6 ms ($n = 100$). Strong recurrence of spikes caused by the intrinsic network structure may also contribute to the longer duration (> 300). However, this cannot explain the difference between these conditions. Thus, the results suggest that sustained neuronal firing, as a result of astrocytic depolarizing currents, plays a major role in the occurrence of synchronous UP states.

Fig. 8 Raster plot of firing activity following synchronous firing of pyramidal cells. Pyramidal cells (2%, nos. 1–192) were programmed to fire at the same time

4 Discussion

The results of our computer simulations, using a mathematical model of neurons and an astrocyte, showed that astrocytic release of glutamic acid and synaptic coupling mediate a synchronous and continuous UP state, lasting several hundred milliseconds, in a group of neurons even if they are not directly influenced by the astrocyte. On the other hand, brief firing activity, mostly lasting only tens of milliseconds, was observed when some neurons

Fig. 9 Histogram of durations of sustained firings following a depolarizing astrocytic current (SIC) or neuronal stimuli without SIC (No SIC)

were forcibly fired simultaneously. This implies that persistent astrocyte activity, which lasts longer than that of neurons, contributes to synchronous UP states, lasting several hundred milliseconds. Neurons in UP states receiving excitatory stimuli from other neurons contribute to other neurons' firing activity via recursive connections, which leads to simultaneous UP states and firings. Since an UP state seems to be prepared to fire close to a threshold value, they are thought to be prepared for information processing such as an attractor in a dynamical system [23]. The present study supports the possibility that astrocytes are involved in the generation of UP states. If this hypothesis is correct, then the generation and maintenance of UP states in a neural network would be a way by which astrocytes contribute to neural information processing.

Self-sustained activity, whereby firing activity is sustained even without continuous external stimuli, has been reported in both mathematical models and physiological experiments [28, 34, 36]. The UP states in the present study, which were maintained even after decreases in astrocyte activity, could be considered a type of self-sustained activity. Neural networks that contain more cells reportedly generate and maintain self-sustained activity more readily [34, 37]. In studying the magnitude of minimal synaptic conductance at which self-sustained activity can be generated in an integrate-and-fire neural network of synaptic connections, El Boustani et al. showed that neural networks with large numbers of neurons generated more self-sustained activity, even at lower synaptic conductance, than when the number of neurons was smaller [38]. The magnitude of EPSPs (approx. 3 mV) induced by a synaptic conductance used in the present study was greater than the mean EPSP value (≈ 1 mV) [39]. Since more neurons with more connections can compensate for slightly smaller EPSP amplitudes as described above, our substantial results will not change in a larger neural network even if the conductances are as small as the physiological data.

On the other hand, a future problem is to elucidate the effect on UP states when bidirectional astrocyte-neuron communication including pathways from neurons to astrocytes is taken into account as mentioned at the end of the Introduction. To model this bidirectional processing based on experimental data [25, 27], we should clarify at least three problems: First, in an astrocyte, how to implement the density of Ca^{2+} , which increases depending on the increase of endocannabinoids by action potentials and determines the density of released glutamate. Second, in the presynaptic site, how to implement the synaptic modulation that evokes potentiation for astrocyte-released glutamate but depression for endocannabinoids. This problem includes the issue that the synaptic modulation is not an amplitude modulation but a modulation in the probability of neurotransmitter release. Third, as a network consists of neurons and astrocytes, how to design the spatial structure, especially the spread range of endocannabinoids from neurons and glutamate from astrocytes. This is an important factor, because whether the potentiation or depression occurs actually depends on the distance from the firing neuron [27]. Furthermore, it is possible to consider signal transmission between astrocytes through gap junctions [40]. If we can construct a mathematical model that settles these issues and execute computer simulations with various parameter values, we will be able to obtain strong indications about the role of astrocytes on neuronal transmission in the interactive astrocyte-neuron network.

5 Conclusion

Computer simulations, using a mathematical model of neurons and an astrocyte, showed that depolarizing astrocytic currents to neighboring neurons synchronously trigger UP states

that persist for several hundred milliseconds, even in neurons not directly influenced by the astrocyte. This result shows that the direct influence of astrocytes is propagated by synaptic coupling in the neural network model, triggering synchronous UP states in a broader range of neurons. On the other hand, if multiple neurons were made to fire synchronously, firing activity was not maintained. These results suggest that the continuous astrocytic activity, lasting several hundred milliseconds, may contribute to the continuous occurrence of UP states in the actual neural network.

Since UP states are thought to be involved in working memory and other information processing, astrocytes may set the stage for neural information processing, maintaining the cell assembly UP state for several hundreds of milliseconds.

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