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The hippocampal beta rhythm and the computational model

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Abstract– Hippocampal beta rhythm is involved in the memory consolidation. Cholinergic projections from the septum are involved in the generation of the rhythm. But the induction mechanism has not yet been clarified. With the application of carbachol a cholinergic agent can induce the intermittent burst of beta rhythm in a hippocampal slice. We have proposed the minimal model consisting of pyramidal and inhibitory neurons and an astrocyte. The minimal model induced the intermittent burst of beta rhythm. These results suggest that carbachol-induced bursts of beta oscillation can be induced by the minimal network model. The astrocytes can contribute to the generation of beta rhythm.

1. Introduction

Hippocampal network induces many kinds of rhythms. Theta, beta and gamma rhythms can be seen in hippocampus [1-3]. Theta and beta rhythms are related to the memory process. It is thought that theta rhythm is related to encode the memory [4], and beta rhythm is related to retrieve the memory [5].

The hippocampal network also induces the epileptiform discharges, which are induced by synchronized neural activity of hippocampal neurons including the pyramidal and inhibitory neurons. The astrocytes are also involved in the generation of the epileptiform discharges as well as the hippocampal pyramidal and the inhibitory neurons [6]. Hippocampal astrocytes have some neurotransmitter receptors as well as neurons do [7]. The activation of the receptors leads to the production of a second messenger inositol tri-phosphate (IP_3) [8]. Intracellular IP_3 leads to the release of Ca^{2+} from intracellular Ca^{2+} stores. The rise of the concentration of Ca^{2+} ($[Ca^{2+}]i$) induces the release of the neurotransmitter [9]. Computational study has been widely used for understanding the dynamics of the discharges [10, 11]. In the studies, the mechanism of the synchronization of the pyramidal and inhibitory neurons and the information transmission are studied [10, 11]. Astrocytes induce the burst-like spikes of neurons. Recently it is assumed that the hippocampal astrocytes may be involved in the generation of theta rhythm [12].

Carbachol, an acetylcholine (ACh) receptor agonist, induces beta rhythms in rat hippocampal slices [13]. During the carbachol-induced beta oscillation, the rapid discharges within the beta frequency range interspersed with quiescent periods. The carbachol-induced beta rhythm shows bursting behavior. In a burst, the potential oscillations have a frequency of 13-20 Hz. The inter-burst interval is 12-50 seconds. The duration of the burst is 5-9 seconds. The mechanism for the induction of the bursts of the beta rhythms remains unknown. The quiescent periods of the carbachol-induced beta oscillation range to a few tens of seconds. There is no ion channels which open for such a long time. One of the glial cells an astrocyte has $[Ca^{2+}]i$ oscillations with periods of a few tens of seconds [14]. Hence, the astrocytes may contribute to the generation of the bursts of beta oscillations.

In the present study, we have simulated the burst of beta oscillations induced in the minimal network consisting of a hippocampal pyramidal, an inhibitory neurons with an astrocyte.

2. Materials and Methods

2.1. Carbachol-induced beta rhythm

Hippocampal slices were prepared from male Wistar rats (45–120 g) aged 3–6 weeks, supplied by Kyudo Co., Japan. The experimental procedures used in this study were approved by the Committee for the Animal Care and Use of Laboratory Animals at the Graduate School of Life Science and System Engineering of Kyushu Institute of Technology (KIT). The experiments were performed under the control of the Ethics Committee of Animal Care and Experimentation in accordance with the Guiding Principles for Animal Care Experimentation, KIT, Japan, and with the Japanese Law for Animal Welfare and Care. The rats were anaesthetized with isoflurane and then decapitated. Their brains were removed quickly and cooled in artificial cerebrospinal fluid (ACSF) solution at 0 ºC. Transverse hippocampal slices, which were 450 μm thick, were prepared using a tissue slicer (Micro Slicer Zero-1, Dosaka-EM Co., Japan). The slices were incubated in an interface-type recording chamber. ACSF solution bubbled with 95% O_2–5% CO_2 was applied for at least an hour. Carbachol-induced beta oscillation was recorded extracellularly from the cell layer and synaptic layer of the CA3 region using a glass microelectrode. The mean frequency was calculated for 1 second after the onset of the burst.

2.2. Computational study

Schematic diagram of the proposed model is shown in Fig. 1. The model consists of a pyramidal, and an inhibitory neuron and an astrocyte. The neural network

model is based on the model proposed by Tang et al (2013). Tang's model has two Hodgkin-Huxley models [11], while our model has a modified Pinsky-Rinzel model [15] as the pyramidal neuron (PY), and Hodgkin-Huxley (HH) model [16] as the inhibitory neuron (IN). The astrocyte (AS) is based on the model by Tang [11].

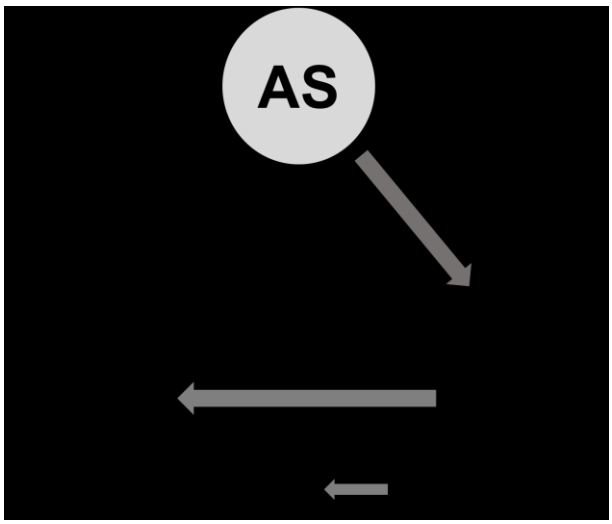

Fig. 1. Schematic diagram of the neuron and astrocyte minimal network model. T1 and T2 are the concentrations of neurotransmitter released by PY and IN, respectively. The synaptic currents induced in PY and IN are Is_1 and Is_2, respectively. The astrocytic currents in PY and IN are I_{AS1} and I_{AS2}, respectively.

The elevation of AS[Ca^{2+}]i results in the release of glutamate from AS [17]. Numerous physiological studies show that glutamate from astrocytes has direct inhibitory effects on hippocampal interneurons [18]. By contrast, astrocytes facilitate the neuronal excitability of the pyramidal neurons via AMPA and N-methyl-D-aspartate glutamate receptors [19, 20]. The effects are different from the Tang's model (2013).

3. Results

3.1. Carbachol-induced beta rhythm

Thirty μM carbachol induced the intermittent bursts of beta rhythm in a rat hippocampal slice as shown in Fig. 2. The field potential was recorded as the negative deflection at the cell layer. The negative deflection recorded extracellularly there reflects the population spike [21]. Thus the hippocampal pyramidal cell fired with beta frequency in a burst and the burst occurred intermittently with a few ten seconds. The frequency in the burst was 16.1 ± 0.4 Hz (mean ± standard errors of the mean (s.e.m.; n = 5 slices from different rats), the duration of the burst is 8.8 ± 0.6 sec, and inter-burst interval (IBI) was 20.0 ± 1.1 sec. The frequency was not constant in a burst. The frequency increased first from the one below 15 Hz and rapidly reached to the top at around 20 Hz, and then it gradually decreased.

3.2. Computational study

In the previous reports [11], the oscillation of AS[Ca^{2+}]$_i$ was controlled by astrocytic [IP_3]$_i$ (AS[IP_3]$_i$). The amplitude of AS[Ca^{2+}]$_i$ oscillation was tracked with the use of the software package XPPAUT [22]. The bifurcation diagram of the astrocyte model is shown in Fig. 3. When AS[IP_3]$_i$ increases, the [Ca^{2+}]$_i$ oscillation appeared via a Hopf bifurcation at 0.32 μM of AS[IP_3]$_i$, and disappeared via the bifurcation at 0.56 μM. The similar bifurcation diagram was reported in the previous study [23]. The astrocytic [Ca^{2+}]$_i$ oscillations have larger amplitude with the increase in AS[IP_3]$_i$ until 0.56 μM (Fig. 3).

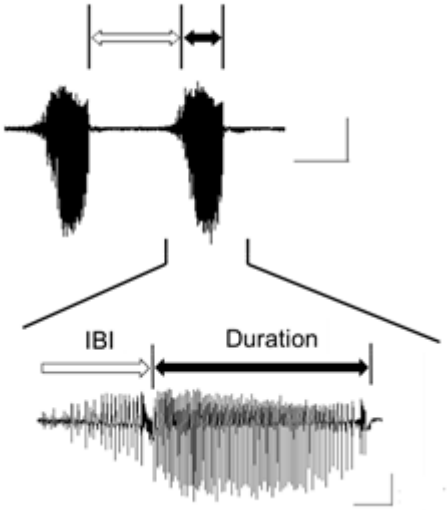

Fig. 2. Experimental results. The signal indicates the extracellular signals recorded in a hippocampal slice. The inter-burst interval is defined as the interval between the burst indicated by the empty double arrow, and the duration is defined as the time duration indicated by the filled double arrow**.** Top: view. Calibration: 10s and 1mV. Bottom: enlarged view. Calibration: 1s and 1mV.

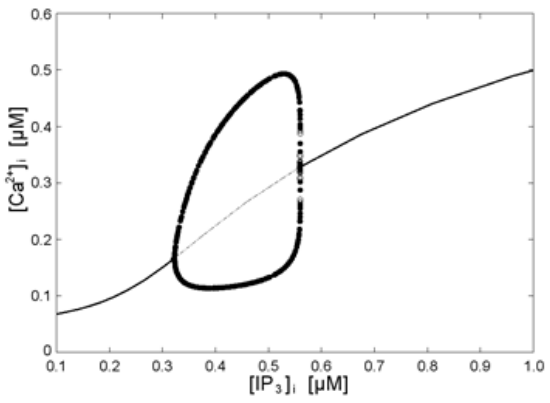

Fig. 3. Bifurcation diagram of astrocyte model. Bifurcation points are 0.3229 and 0.5596 for $[IP_3]i$. Solid line indicates the stable steady state and a dashed line indicates the unstable steady state.

The hippocampal PY, IN and AS are connected as shown in Fig. 1. The simulation results of PY in the network are shown in Fig. 4. PY began to fire with slower frequency and then fired as a burst (Fig. 4(a)). The burst stopped and after 20 seconds PY began to fire with slower frequency and the burst appeared once again. So, PY fired as an intermittent burst. IN also began to fire with slower frequency and fired as a burst like PY. PY induced spikes of IN followed by a long plateau and a small extra spikes. After that the spike amplitude recovered at the end of a burst. Spikes of IN were entrained by PY firings. Even if IN had a smaller amplitude in a burst, it fired synchronously with PY.

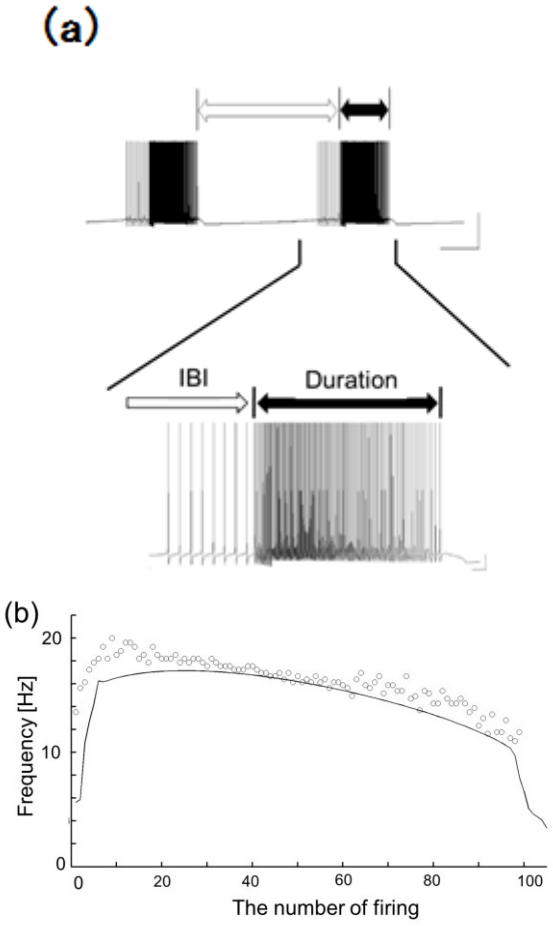

Fig. 4. Simulation results of the pyramidal cell membrane potential . (a) Top: the membrane potential of PY. Calibration: 10s and 20 mV. Bottom: enlarged view. Calibration: 1s and 10mV. (b) Comparison of the temporal changes of frequency in a burst. The circles indicate the frequency of the firing in a burst. Solid line indicate the simulation result.

The mean frequency of the firing of PY in a burst is 17.1 Hz, thus the frequency is in the beta frequency range. The duration of the burst was 8.36 ± 0.03 sec and IBI was 34.50 ± 0.02 sec. The frequency in a burst gradually increased for 1.81 ± 0.02 sec (n = 3 trials), reached to the top, and then gradually decreased (Fig. 4(b)). The time course of the frequency in a burst is similar to that recorded in the physiological experiment shown.

4. Discussion

In the present model, we proposed the beta oscillation model after the application of carbachol, that is, after changing the channel parameters. It is also reported that carbachol induces the depolarization of the membrane potential and the inhibition of the synaptic potentials [24]. We assumed that the present model represents the cellular characteristics and network behavior, and an astrocyte.

Carbachol induced the beta oscillations in a hippocampal network [13, 25]. It was confirmed that they occur like bursts in the physiological experiment (Fig. 2). In the present study, the proposed model could reproduce the bursts of the oscillations (Fig. 4). The results also showed that the duration and the frequency are similar to that physiological results. Only IBI was the outlier of the present experimental data. In the previous results [13], however, the IBI has the range between 12 and 50 seconds, which includes the present experimental data. Hence, the proposed computational model can be plausible.

The present minimal neuro-astrocyte network model reproduced the bursts of beta oscillation in hippocampal slice preparations. In the model, the synchronized firings of PY and IN are critical to induce the burst of the beta oscillation. PY and IN fire synchronously, they release the neurotransmitter glutamate and GABA in the synaptic cleft, then AS receives them through the metabotropic receptor, mGluR and $GABA_B$ receptors, and in results the production rate of $AS[IP_3]_i$ increases. Accompanying with it, $AS[Ca^{2+}]_i$ also gradually increases. $AS[Ca^{2+}]_i$ increases above 0.196 μM, and the astrocytic currents (I_{astro}) in PY and IN begin to flow in PY and IN. I_{astro} in PY is an inward current and I_{astro} in IN is an outward one. In results, repetitive discharges of PY are facilitated and IN has a smaller action potentials, then the inhibitory synaptic current is weaker. The increase in the firing rate of PY and IN leads to release glutamate and GABA more. In results, the increase in the slope of $AS[IP_3]_i$ become steeper. The astrocytic currents in PY and IN increases with the increase in $[Ca^{2+}]i$. When $AS[IP_3]_i$ exceeds the threshold of the generation of $AS[Ca^{2+}]i$ oscillation at 0.32 μM, the oscillation starts (Fig. 3). In $AS[Ca^{2+}]_i$ oscillation, $[Ca^{2+}]_i$ starts to decrease, and I_{astro}'s in both PY and IN decrease, the firing rates of PY and IN decreases. The decrease in the firing rates of PY and IN decreases the production rate of $AS[IP_3]_i$, and in results $AS[IP_3]_i$ decreases below the threshold for the generation of $AS[Ca^{2+}]_i$ oscillation. $AS[Ca^{2+}]_i$ decreases below 0.196 μM, I_{astro}'s stop flowing in PY and IN and finally the burst of beta oscillations

stops. For the termination of the bursts and during IBI of the bursts of beta oscillations, I_{KAHP} was also flowed (data not shown). The currents are involved in the termination of the burst firing of hippocampal pyramidal cells [26].

AS$[Ca^{2+}]_i$ has a slow dynamics and PY and IN have the fast dynamics. In results, the network has the burst phenomena [27].

Acknowledgments

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