Spatial information enhanced by non-spatial information in hippocampal granule cells

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Abstract The hippocampus organizes sequential memory composed of non-spatial information (such as objects and odors) and spatial information (places). The dentate gyrus (DG) in the hippocampus receives two types of information from the lateral and medial entorhinal cortices. Non-spatial and spatial information is delivered respectively to distal and medial dendrites (MDs) of granule cells (GCs) within the molecular layer in the DG. To investigate the role of the association of those two inputs, we measured the response characteristics of distal and MDs of a GC in a rat hippocampal slice and developed a multi-compartment GC model with dynamic synapses; this model reproduces the response characteristics of the dendrites. Upon applying random inputs or input sequences generated by a Markov process to the computational model, it was found that a high-frequency random pulse input to distal dendrites (DDs) and, separately, regular burst inputs to MDs were effective for inducing GC activation. Furthermore, when the random and theta burst inputs were simultaneously applied to the respective dendrites, the pattern discrimination for theta burst input to MDs that caused slight GC activation was enhanced in the presence of random input to DDs. These results suggest that the temporal pattern

discrimination of spatial information is originally involved in a synaptic characteristic in GCs and is enhanced by non-spatial information input to DDs. Consequently, the co-activation of two separate inputs may play a crucial role in the information processing on dendrites of GCs by usefully combining each temporal sequence.

Keywords Dentate gyrus · Granule cell model · Temporal pattern discrimination · Spatial and non-spatial information

Introduction

The hippocampus plays an important role in declarative (episodic) memory (Scoville and Milner 1957). Eichenbaum hypothesized that the network of sequences composed of spatial and non-spatial information consists of episodic memories organized in the hippocampus (Eichenbaum 2004; Eichenbaum et al. 1999). Indeed, it has been reported that a hippocampus-dependent declarative memory (specifically, memory of the positions of cards) is affected by odor cues during sleep (Rasch et al. 2007). This indicates that non-spatial information (such as objects and odor) influence spatial information (places) in hippocampal memory.

From the results of rodent studies, it has recently been reported that when rats pass through a certain place, neurons called “place cells” emit spikes in their hippocampus. Place cells show rhythmic activity with respect to theta waves, which is the oscillation of a local field potential at around 8 Hz (O’Keefe and Recce 1993; Skaggs et al. 1996). The firing phase of a place cell advances to the early phase of the theta rhythm. Many place cells show similar theta phase precession; thus, the sequential activity of place

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cells is kept in the theta cycle. Consequently, the hippocampus can memorize sequences of spatial information. However, non-spatial information is also coded in neuronal activity in the hippocampus (Fortin et al. 2002; Hampson et al. 1999; Moser and Moser 1998). It has been reported that sequences of non-spatial information are also stored in the hippocampus (Fortin et al. 2002).

The hippocampus consists of the DG and regions CA3 and CA1. They receive inputs from the entorhinal cortex (EC) through the perforant pathway. Specifically, a GC in the dorsal hippocampal DG receives inputs from different EC regions through two pathways (Burwell and Amaral 1998; Hjorth-Simonsen 1972; Hjorth-Simonsen and Jeune 1972; McNaughton 1980). One is the lateral perforant path (LPP) from the lateral EC II (LEC) projecting in the outer molecular layer (OML) and distal dendrites (DDs) in the OML. The other is the medial perforant path (MPP) from the medial EC II (MEC) projecting in the middle molecular layer (MML) and medial dendrites (MDs) in the MML. Different information is conveyed through the LEC and MEC pathways (Deshmukh and Knierim 2011; Hargreaves et al. 2005; Yoganarasimha et al. 2011). Non-spatial and spatial information is delivered to a GC in the DG from the LEC and MEC, respectively. LEC neurons respond to non-spatial information [such as objects (Deshmukh and Knierim 2011) and odor (Xu and Wilson 2012; Young et al. 1997)], and their activity is less regular compared with that of MEC neurons (Deshmukh et al. 2010). In contrast, MEC neurons emit brief bursts at theta intervals during explorative behavior and sleep (Alonso and Garcia-Austt 1987; Deshmukh et al. 2010; Jeewajee et al. 2008; Sullivan et al. 2014). Thus, DDs receive random rather than regular pulse inputs from the LEC, whereas MDs receives regular burst inputs from the MEC. This means that GCs are tuned to both non-spatial and spatial information arriving from the EC. The LEC and MEC co-activate during exploration (Deshmukh and Knierim 2011), and GCs receive non-spatial and spatial information simultaneously. Additionally, LPP and MPP activation evoke different responses from the same GC (Colino and Malenka 1993; McNaughton 1980). Paired-pulse stimulation through LPP and MPP evokes facilitation and depression of the excitatory postsynaptic potential (EPSP) on GC, respectively. Non-spatial information on DDs is processed differently from spatial information on GC dendrites depending on the distance from the soma to a DD or an MD. These types of information can interact with each other at a GC. Thus, information processing by GCs in the DG plays a key role in hippocampal memory composed of spatial and non-spatial information. However, the mechanism of association, or how spatial information and non-spatial information interact with each other to form hippocampus-dependent sequential memory, is still unclear.

In this study, to investigate the role of input association at DDs and MDs, we performed an electrophysiological study on rat hippocampal GCs and a computer simulation of a GC model created by fitting parameters for the physiologically obtained data. First, in the physiological experiment, the input characteristics of DDs and MDs were measured for synaptic input trains. Next, in the computational experiments, we developed a multi-compartment GC model with dynamic synapses. In addition, by applying input sequences based on the physiological characteristics of inputs at DDs and MDs obtained in physiological studies (Alonso and Garcia-Austt 1987; Deshmukh et al. 2010) to the computational GC model, we found that high-frequency random pulse input to DDs maximized the response of a GC, and specific burst sequences (modeled by a Markov process) input to MDs effectively activated the response of a GC. Finally, in the computational experiment, to investigate the influence of co-activation of DDs and MDs on information processing in a GC, random pulse input and regular burst input were simultaneously applied to DDs and MDs, respectively. The results showed that non-spatial information input to a DD enhanced spatial information input to an MD on a GC. We will discuss the role of association on the co-activation of inputs to MDs and DDs.

Materials and methods

Slice preparation

All procedures were approved by the Tamagawa University Animal Care and Use Committee. Transverse hippocampal slices (400 μ m thick) were prepared from 3 to 4 week old Wistar rats by using a microslicer (DTK-1000; Dosaka EM Corp., Japan). These slices were perfused with 30 °C artificial cerebrospinal fluid (ACSF) containing 124.0 mM NaCl, 3.0 mM KCl, 1.25 mM $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 2.0 mM $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 2.2 mM NaHCO_3 , 2.5 mM $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, and 10 mM $\text{C}_6\text{H}_{12}\text{O}_6$ and bubbled with 95 % O_2 and 5 % CO_2 in an incubation chamber for 1 h. Next, the slices were transferred to a recording chamber, and extracellular field excitatory postsynaptic potentials (fEPSPs) were recorded from the DG.

Recordings and electrophysiological experiments

Two monopolar glass electrodes filled with ACSF were placed on the OML and MML of the DG to record fEPSPs evoked by pulse trains (Fig. 1a) because the LPP and MPP project to the OML and MML of the DG, respectively (McNaughton 1980). The resistance at the tip of the electrodes was 2–5 M Ω (Colino and Malenka 1993). The

Fig. 1 Response characteristics of MDs and DDs of a GC with respect to a pulse train input.

a Schematic representation of the experimental configuration in the DG. Two recording electrodes were placed on the OML (DD) and MML (MD) to record fEPSP evoked by a five-pulse train input through the LPP and MPP. Two stimulating electrodes were also placed on the layers to stimulate each pathway independently. **b–g** Response characteristics are normalized responses evoked by a pulse train input to each dendrite at a frequency of **(b)** 0.1, **(c)** 1.0, **(d)** 2.0, **(e)** 5.0, **(f)** 10.0, and **(g)** 20.0 Hz. The responses are the peak amplitudes of fEPSPs evoked by each pulse normalized by the first response in each condition. *Solid circles and triangles* indicate responses recorded from DDs and MDs, respectively. The fEPSPs were recorded in the absence (*gray*) or presence (*black*) of picrotoxin

recordings were made with a patch-clamp amplifier (Axopatch 200B, Molecular Devices Corp.), recording software (pCLAMP, Molecular Devices Corp.), and an A/D converter (Digidata 1322A, Molecular Devices Corp.). The recorded waveforms were acquired through a low-pass filter (a Gaussian low-pass filter with a cutoff frequency of 500 Hz in the Clampfit software, Molecular

Devices Corp.). Identical bipolar glass electrodes were placed on the OML and MML for stimulating the LPP and MPP, respectively (Fig. 1a). Stimulation was generated by a stimulator (SEN-7203, Nihon Kohden, Inc.) and an isolator (SS-102J, Nihon Kohden, Inc.). We verified the electrode positions by using paired-pulse stimulation with an inter-stimulus interval of 200 ms. It has been reported

that the LPP and MPP cause paired-pulse facilitation and depression of the fEPSP, respectively (Colino and Malenka 1993).

To investigate the response characteristics of DDs and MDs of a GC to a pulse train, stimuli consisting of a train of five constant voltage pulses (pulse duration of 200 μ s) at frequencies from 0.1 to 20 Hz were applied to the LPP and MPP of a GC, respectively, in the presence or absence of GABA_A receptor antagonist (picrotoxin, 50 μ M). We observed the peak amplitudes of fEPSPs evoked by each pulse of the input. The peak amplitudes were normalized by the fEPSPs evoked by the first pulse of a train.

GC model with dynamic synapses

We developed a multi-compartment GC model with dynamic synapses (Tsodyks et al. 1998) by modifying the Ferrante–Ascoli GC model (Ferrante et al. 2009). Using the NEURON simulator (Hines and Carnevale 1997), 37 compartments were passively connected with other compartments for reconstructing the morphology of an actual GC (32 compartments for dendrites, 4 compartments for a soma, and an axon compartment; Fig. 2a). The soma compartments were constructed using a Hodgkin–Huxley neuron model fitted to experimental data. We put the receptors in each dendrite compartment with dynamic synapses (Tsodyks et al. 1998). We defined dendritic compartments within 140–230 μ m away from a soma compartment as MDs and dendritic compartments more than 270 μ m away from a soma compartment as DDs. MDs and DDs were connected to the MPP and LPP, respectively. Some dendritic compartments were connected to the MPP and/or the LPP, depending on the distance from a soma compartment. Dendritic compartments connected to the MPP or LPP evoked postsynaptic current through dynamic synapses when the compartments received presynaptic spikes. Dynamic synapses (Tsodyks et al. 1998) reproduced transient facilitation and depression of synaptic transmission between the dendritic compartments and presynaptic terminals of the MPP and LPP (MPP and LPP sites). In the dynamic synapse model, a specific amount of neurotransmitter (glutamate) transitions among three states (recovered, active, and inactive). Postsynaptic current is induced depending on the amount of neurotransmitters transiting to the active state. The postsynaptic current of the i th dendritic compartment was calculated from the following equation:

$$I_i(t) = g_i(t)(V - V_{in}), \quad (1)$$

where $V_{in}(=0$ mV) is a reversal potential for postsynaptic current and $g_i(t)$ is synaptic conductance given by

$$\frac{dg_i(t)}{dt} = -\frac{g_i(t)}{\tau_{in}} + w_i u_i(t) x_i(t) \delta(t - t_{AP}), \quad (2)$$

where w_i is the synaptic weight of a perforant path synapse and $x_i(t)$ indicates the number of neurotransmitters in the recovered state. $u_i(t)x_i(t)$ indicates the amount of neurotransmitter released from perforant path ($y_i(t)$ corresponds to it). $u_i(t)$ is described later in this section. $\delta(\cdot)$ is the Dirac delta function and represents the arrival time of input pulses mimicking spikes coming from the EC. The transition of the neurotransmitter of the i th dendritic compartment is governed by the following equations:

$$\frac{dx_i(t)}{dt} = \frac{z_i(t)}{\tau_{rec}} - u_i(t)x_i(t)\delta(t - t_{AP}), \quad (3)$$

$$\frac{dy_i(t)}{dt} = -\frac{y_i(t)}{\tau_{in}} + u_i(t)x_i(t)\delta(t - t_{AP}), \quad (4)$$

$$\frac{dz_i(t)}{dt} = -\frac{z_i(t)}{\tau_{rec}} + \frac{y_i(t)}{\tau_{in}}, \quad (5)$$

where $x_i(t)$, $y_i(t)$, and $z_i(t)$ indicate the amount of neurotransmitter in the recovered, active, and inactive states, respectively, τ_{rec} and τ_{in} are time constants for the state transitions, and $u_i(t)$ indicates the open channel ratio calculated as follows:

$$\frac{du_i(t)}{dt} = -\frac{u_i(t)}{\tau_{facil}} + U(1.0 - u_i(t))\delta(t - t_{AP}), \quad (6)$$

where τ_{facil} indicates the time constant for channel closure. U indicates the increase of the ratio by an arriving spike.

Computational experiments

After the electrophysiological experiments, we performed four computational experiments with the NEURON simulator (Hines and Carnevale 1997).

In the first computational experiment, we reproduced the response characteristic of DDs and MDs of a GC evoked by a 5-pulse train in the presence of picrotoxin. Fifty MPP and LPP sites each were selected at random. The same pulse train as that used in the electrophysiological experiments was applied individually to the DDs and MDs of the GC cell model (Fig. 2a). The peak amplitudes of EPSPs evoked by each pulse were obtained from a soma compartment. The synaptic weights (w_i) of all DDs and MDs were set to 0.0003. We fitted the parameters for the dynamic synapse of DDs and MDs to bring the peak amplitudes of the soma EPSP to a level similar to those of fEPSPs. The model constructed by those parameters was used without inhibitory input in all computational experiments.

In the second computational experiment, we investigated the responses of DDs and MDs of a GC to random

Fig. 2 Reproduction of the responses of DDs and MDs. **a** Dendritic arborization of a GC model. Dendrite is divided into DD and MD based on their distance from a soma compartment. *Dots* indicate the placements of the synaptic connections on the DD (*blue*) and MD (*red*). **b–g** Response characteristics of DDs and MDs of an actual GC (*solid circles* and *triangles*) and a GC model (*open circles* and *triangles*) represented as normalized responses evoked by a pulse train to each dendrite at a frequency of (**b**) 0.1, (**c**) 1.0, (**d**) 2.0, (**e**) 5.0, (**f**) 10.0, and (**g**) 20.0 Hz. The responses of the actual GC are the peaks of fEPSPs evoked by each pulse under the presence of picrotoxin in Fig. 1 (**b–g**). The responses of the GC model are the peaks of EPSPs recorded from a soma compartment. Responses evoked by a train are normalized by the first response in each case. (Color figure online)

pulse inputs. The average frequencies of inputs were 0.1, 1, 5, 10, and 20 Hz (Fig. 3a), with an inter-pulse interval obeying a Poisson distribution. Random pulse inputs were applied for 2 s to 500 sites selected at random from the MDs and DDs of a GC model, respectively. Each site received a different random pulse input with the same average frequency. The synaptic weights of DDs and MDs were set to 0.00008 and 0.00005 of that with which sub-

threshold response were induced by those 500 synapses, respectively. We measured the change in membrane potential of the soma compartments as the responses of a GC to each dendritic input.

In the third computational experiment, random pulse inputs generated by a Markov process were applied to MDs to investigate the responses of MDs to a temporal pattern (burst input). The intervals between pulses were derived

Fig. 3 Responses of DDs and MDs to random pulse inputs. **a** Random pulse inputs were generated from a Poisson distribution at different average frequencies in the range of 0.1–20 Hz. **b**,

c Responses of a GC to the random pulse inputs applied to **(b)** DDs and **(c)** MDs for 2 s, respectively. The response of the GC model was taken as the membrane potential obtained from a soma compartment

from a Markov process with two states (short and long intervals) (Fig. 4a, left panel). The transition probability (P) between the states was changed in the range of 0.1–0.9. The output corresponding to each state indicates the interval between spikes. The output of the short interval state (S) was changed in the range of 5–25 ms, and that of the long interval state (L) was 500, 250, 125, or 83 ms (2, 4, 8, or 12 Hz, respectively). The temporal patterns (burst inputs) generated by the Markov process changed from regular to irregular according to the probability (P) (Fig. 4a, right panel). The synaptic weights used for MDs were 0.125 (weak), 0.20 (medium), and 0.25 (strong) of that with which spikes (supra-threshold response) were induced by 100 synapses. In addition, those firings were suppressed by the EPSP depression in steady state. For each parameter set, a Markov random pulse input with 50 long intervals was applied to 100 dendrites selected at random from among the MDs. The response of a GC to the burst input was evaluated by the ratio of emitted spikes to input pulses (I/O ratio).

Finally, we investigated the response of a GC to concurrent pulse inputs to MDs and DDs. Regular burst inputs and random pulses were applied to MDs and DDs, respectively (Fig. 5a). The random pulse inputs were the same as in the second simulation. The average frequencies of the inputs were 10 or 20 Hz. The regular burst inputs were defined by three parameters: the number of pulses in a burst (n), the inter-burst interval (IBI), and the inter-stimulus interval (ISI) in a burst. The number of pulses in a

burst (n) changed in the range of 1–5, IBI was 125 ms (8 Hz), and ISI changed in the range of 5–25 ms. These inputs were applied for 5 s. The synaptic weights of the DDs and MDs were set to 0.11 and 0.2 (medium), respectively. The response of a GC to the burst input was evaluated by the ratio of the emitted spikes to the MPP input pulses (I/O ratio).

Results

Response characteristics of DDs and MDs in electrophysiological experiments

A pulse train consisting of 5 pulses was applied to DDs and MDs of a GC through the LPP and MPP, respectively (Fig. 1a). The input frequency changed in the range of 0.1–10 Hz in the presence or absence of a GABA_A receptor antagonist (picrotoxin). The responses of DDs and MDs were the same regardless of the presence of picrotoxin in the case of the 0.1-Hz pulse train (Fig. 1b). However, there were apparent differences between the responses of DDs and MDs when the input frequency was more than 1 Hz (Fig. 1c–g).

Although the fEPSP amplitudes of DDs were maintained in the case of moderate input frequency (1–5 Hz) (Fig. 1b–e), the fEPSP amplitudes decreased when high-frequency input (10 and 20 Hz) was applied (Fig. 1f, g). However, picrotoxin eliminated the depression effect and

Fig. 4 Responses of a GC model to burst inputs applied to MDs. **a** Burst inputs were generated by a Markov random process with short (S) and long (L) interval states (**a**, left panel). The intervals between spikes changed according to the output of each state, and the regularity of a generated burst input changed according to a probability P (**a**, right panel). Although two-pulse bursts occurred almost constantly at low values of P , multi-pulse bursts occurred irregularly at large values of P . **b–d** Responses to various burst inputs

with 50 long intervals applied to MD of a GC model through **(b)** weak, **(c)** medium, and **(d)** strong MPP synapses. Various burst inputs were generated by changing three parameters: S (5–25 ms), L [83–500 ms (2–12 Hz)], and P (0.1–0.9). The response is the ratio of output spikes to input spikes (I/O ratio). **e** Differences in I/O ratio between responses for strong and medium MPP synapse weight strength (panel 1 in Fig. 4c, d)

facilitated the fEPSPs evoked by the second pulse in 10-Hz and 20-Hz inputs. In contrast, MDs showed a depression of fEPSP amplitude regardless of the input frequency and the presence of picrotoxin (Fig. 1c–g). The fEPSP amplitudes evoked by pulses following the first pulse decreased in all cases.

Although the response of DDs was depressed by inhibitory inputs at only 10–20 Hz, DDs and MDs showed sustained and transient responses regardless of the presence or absence of picrotoxin, an antagonist of GABA_A receptors. These results indicate that the differences between the responses of MDs and DDs are not due to inhibition but

Fig. 5 Response of a GC model to concurrent pulse inputs applied to MDs and DDs.

a Random pulse and regular burst pulse inputs are applied to DDs and MDs, respectively. **b–d** Response of a GC model to (b) regular burst inputs only, (c) 10 Hz random pulse + regular burst inputs, and (d) 20 Hz random pulse + regular burst inputs applied for 5 s. Different burst inputs are generated by changing two parameters: ISI (5–25 ms) and n (1–5). IBI is fixed at 125 ms (8 Hz). The response is the ratio of output spikes to MPP input spikes (I/O ratio)

Table 1 Parameters for LPP and MPP sites

	LPP site	MPP site
τ_{rec} (ms)	248	3977
τ_{in} (ms)	1	1
τ_{fascil} (ms)	133	27
U	0.2	0.3

rather due to the different dynamics of LPP and MPP synapses. Therefore, we constructed a model without inhibitory inputs and the response characteristics at GCs were measured in computational experiments.

Reproduction of the responses of DDs and MDs

We reproduced the responses of DDs and MDs in the presence of picrotoxin by fitting the parameters for dynamic synapses of DDs and MDs (LPP and MPP sites) of a GC model as shown in Table 1 (Fig. 2). Similar responses of DDs and MDs of a GC were evoked by the same pulse train (Fig. 1a). MDs showed depression of EPSP when the input frequency was over 1 Hz (Fig. 2c–f). In contrast, DDs showed facilitation of EPSP evoked by the second pulse depending on the input frequency (Fig. 2f–g).

MPP sites had a large time constant for the transition from inactive state to recovered state (τ_{rec}) compared to that of LPP sites. Once released from MPP synapses, neurotransmitters require a long time to be recovered. Furthermore, MPP sites have a small time constant for channel closure (τ_{fascil}). These characteristics mean that the release of neurotransmitters through channels on MPP synapses is temporally limited. Consequently, the pulse train drains MPP synapses of neurotransmitters and causes depression of EPSP. Conversely, the pulse train causes facilitation of EPSP at DDs because neurotransmitters recovered quickly and the channels close slowly.

Sustained and transient responses of DDs and MDs to random pulse inputs

Random pulse inputs obeying a Poisson distribution were applied to a GC model (Fig. 3a). The average frequency of the inputs was changed in the range of 0.1–20 Hz. DDs show a sustained response according to the input frequency (Fig. 3b). High-frequency inputs resulted in a high membrane potential that was maintained for the duration of the input. In contrast, in MDs, high-frequency inputs transiently induced a high membrane potential at the onset of

the input, but the membrane potential decreased rapidly on the same time scale, regardless of the input frequency (Fig. 3c). Therefore, high-frequency persistent random pulse inputs to DDs maximize the response of a GC. In contrast, the response of a GC is maximized by intermittent high-frequency burst inputs to MDs.

Responses of MDs to burst inputs depending on synaptic weight

To determine what temporal patterns (burst inputs) to MDs are effective for inducing GC activation, various burst input sequences generated by a Markov process with two states (Fig. 4a, left panel) were applied to MDs through MPP synapses with three weights (strong, medium, and weak, with the same values given above). In a burst input, some of the regularly spaced pulses of a periodic pulse train were replaced by various burst pulses, with 2, 3, or more pulses in a burst (Fig. 4a, right panel). A short interval S and a long interval L were adopted for the inter-pulse interval in a burst and the inter-burst interval, respectively. To investigate the effects of depression, the long interval (L) was changed in the range 83–500 ms (2, 4, 8, 12 Hz) around the theta frequency since 1–2 Hz induced a weak depression and 10–20 Hz induced strong depression (Fig. 2) and the input-firing frequency from MEC was in the theta rhythm (4–8 Hz).

For weak weights ($w = 0.125$), burst inputs with $L = 500$ ms (2 Hz) induced strong GC activation and I/O ratio for S shorter than 15 ms (Fig. 4b, panel 1). The GC activation weakened with increasing the P value from 0.1 to 0.9. However, for burst inputs with $L = 250$ ms (4 Hz) (Fig. 4b, panel 2), GC activation was weaker at low P values (0.1–0.3) but remained high at medium P values in the range of 0.4–0.8 for burst inputs with 3 or more pulses. In comparison, the activation was weak at the high P of 0.9, which corresponded to inputs consisting of mostly single pulses with few long-lasting bursts. The result suggests that suitable inputs consisting of 2, 3, or more pulses with a parameter $P = 0.3$ to 0.8 (Fig. 4b, panel 2) in a burst are required to activate a GC because of the strong depression of the EPSP of the successive inputs (MD response in Fig. 2d–g). The GC was not activated for $L = 125$ and 83 ms (8 and 12 Hz) (Fig. 4b, panels 3 and 4).

For medium weights ($w = 0.20$), the burst inputs with $L = 500$ and 250 ms (2 and 4 Hz) induced strong GC activation for S shorter than 20 and 12 ms, respectively (Fig. 4c, panels 1, 2). The activation also decreased with increasing the P value from 0.1 to 0.9, similarly to the case of weak synaptic weight ($w = 0.125$) at 2 Hz (Fig. 4b, panel 1). In addition, in the case of the burst inputs with $L = 125$ ms (8 Hz) (Fig. 4c, panel 3), the GC activation

decreased at low P values (0.1–0.3) but remained high at medium P values (0.4–0.8). The activation was low at the high P of 0.9, which corresponded to the result for $w = 0.125$ at 4 Hz in Fig. 4b. Moreover, the activation of GC was depressed at $L = 83$ ms (12 Hz) (Fig. 4c, panel 4).

For strong weights ($w = 0.25$), burst inputs with $L = 500$ and 250 ms (2 and 4 Hz) induced strong GC activation for S shorter than 23 and 16 ms (Fig. 4d, panels 1 and 2, respectively). The activation decreased with increasing P . In contrast, for burst inputs with $L = 125$ and 83 ms (8 and 12 Hz) (Fig. 4c, panels 3, 4), GC activation appeared at only suitable burst input patterns, which was not observed in the case of weak synaptic weights ($w = 0.125$) at 8–12 Hz (Fig. 4b, panels 3, 4).

The results suggest that the frequency range for inducing a GC response to burst inputs can be expanded by increasing the synaptic weights, even though all burst inputs generated by the Markov process induced EPSP depression that was more pronounced at shorter pulse intervals. On the other hand, the 2-Hz stimulation was most effective for activating GCs. However, Alonso and Garcia-Austt (1987) and Deshmukh et al. (2010) have reported a theta rhythm for the MEC cell firing frequency. Therefore, it is expected that 2-Hz inputs would not usually be served in the MD. In addition, all temporal patterns (burst pattern) activated GC neurons at 2 Hz, showing no selectivity for input temporal patterns. In contrast, input selectivity was observed in a suitable burst pattern over the frequency range around the theta frequency [weak, 4 Hz (panel 2); medium, 8 Hz (panel 3); strong, 8–12 Hz (panels 3 and 4)]. These results show that there is a temporal pattern sensitivity for bursting inputs at the theta frequency.

Furthermore, the input range that activates a GC is expanded by increasing the synaptic weight. Figure 4e shows difference in I/O ratios between responses to medium and strong synaptic weights at 2 Hz (panel 1 in Fig. 4c, d, respectively). Although the response to burst inputs was expanded, particularly at low P , for S of 20–23 ms when the synaptic weight was changed from medium to strong, the I/O ratios for $P = 0.9$ consisting of many single inputs were not increased. These results suggest that single pulse inputs alone are unable to activate GCs.

Response of MDs to regular burst inputs enhanced by random pulse inputs to DDs

We found that both persistent high-frequency inputs to DDs and specific regular burst inputs to MDs are separately effective in inducing GC activation. These response characteristics were consistent with the activity in the LEC and MEC (Deshmukh et al. 2010). This suggests that GCs are optimized to react to inputs from either the LEC or the

MEC. However, the LEC and MEC activate simultaneously in a rat (Deshmukh and Knierim 2011). To investigate how the two inputs interact with each other and co-activate a GC, random pulses (obeying a Poisson distribution) and regular burst inputs were applied to DDs and MDs, respectively (Fig. 5a). At each strength of synaptic weights (Fig. 4b–d), the GC was activated over a wide range of input frequencies (2–12 Hz) at medium P values from 0.4 to 0.8. In comparison, at the high P of 0.9, GC activation was depressed at frequencies in the theta range (8 Hz). Interestingly, sensitivity to the burst pattern at 8 Hz was not clearly observed in the case of weak synaptic weights ($w = 0.125$, Fig. 4b, panel 3) but was strongly observed in the case of strong synaptic weights ($w = 0.25$, Fig. 4d, panel 3). Here, we applied burst inputs at 8 Hz to MDs using medium synaptic weights ($w = 0.2$), which moderately activate GC neurons by themselves. Moreover, additional Poisson random inputs were simultaneously applied at 10 or 20 Hz to DDs (Fig. 5b–d). Moderate responses were observed in the firing of a GC for $n = 2$ –5 and ISI = 5–20 ms when regular burst inputs were applied to MDs alone. The sensitivity for burst inputs did not show a clear pattern. In addition, when 10-Hz random pulse inputs were simultaneously applied to DDs (Fig. 5c), GC activation for regular burst inputs was facilitated, and a specific burst pattern was observed at $n = 3$ –4 and ISI = 7–8 ms. Moreover, additional 20 Hz random pulse inputs applied simultaneously further facilitated the GC activity in Fig. 5d. Enhancement due to simultaneous application of DD inputs was limited in a specific burst pattern, namely theta burst with $n = 2$ –5 (especially for $n = 3$ and 4) at around 8 Hz. These results indicate that random pulse inputs applied to DDs enhance and tune the input burst pattern to MDs contributing to activation of a GC, suggesting that co-activation of DDs is an important factor in frequency filtering of MD input.

Discussion

We showed the response characteristics of DDs and MDs of a GC to pulse train input in electrophysiological experiments and developed a GC model with dynamic synapses that reproduced the response characteristics. From parameters fixed in the model (Table 1), the recovery capacity of neurotransmitters is low at the presynaptic terminal in the MD-MPP synapse because of the large time constant for the transition from the inactive state to the recovered state (τ_{rec}), meaning that the cells are prone to depletion of neurotransmitter at the presynapse. On the other hand, release of neurotransmitter is facilitated at the presynaptic terminal in the DD-LPP synapse because of the small time constant for channel closure (τ_{facil}). Therefore,

different responses to the paired-pulse responses were observed at the two synapses. Moreover, using a computer simulation, we derived the inputs to DDs and MDs that effectively induce GC activation. As a result, we found that high-frequency random input to DDs maximizes the response of the GC. Conversely, regular burst input to MDs effectively induced GC activation because of the transient response of MDs to persistent random input. In fact, an actual GC receives inputs through the LPP and MPP synapses (Alonso and Garcia-Austt 1987; Deshmukh et al. 2010; Igarashi et al. 2007) that are consistent with the inputs to each dendrite that activate a GC. LEC neurons show irregular activity compared to MEC neurons (Deshmukh et al. 2010), which in turn show regular burst input at theta intervals (Alonso and Garcia-Austt 1987; Deshmukh et al. 2010). Based on these neuronal activities of the LEC and MEC, the DDs and MDs of a GC receive random pulse and regular burst inputs from the LEC and MEC, respectively. In other words, we found that DD and MD synapses are tuned to inputs from the LEC and MEC in those two synaptic characteristics. Furthermore, the response of a GC to regular burst inputs to MDs was enhanced by random pulse inputs to DDs. A GC reacts selectively to regular burst inputs at specific intervals. Thus, MD synapses of a GC may function as a band-pass filter that passes regular burst inputs (such as theta bursts) and DD synapses serve the function of a filter for MDs by boosting the signal in the soma. These distinct mechanisms are due to the different properties of the DD and MD. The activation of GCs depends on the input rate at the DD, not at the MD (Fig. 4), so that the DD is used for coding input rate and the MD is used for coding input timing (temporal pattern, coincidence). Therefore, random input to DD increases the activity of GCs as a bias effect and the responses of GCs for temporal patterns (theta bursts presenting as population activity) to the MD are effectively enhanced DD inputs (Fig. 5b–d). In fact, a GC selectively reacts to inputs at theta frequency (Ishizuka et al. 2004). Our results suggest that a band-pass filter is effectively constructed depending on the temporal properties in information processing of two synaptic pathways.

In the two pathways that convey spatial and non-spatial information from the EC (Deshmukh and Knierim 2011; Hargreaves et al. 2005; Yoganarasimha et al. 2011), non-spatial information was encoded depending on the frequency in random inputs (Fig. 3b), and spatial information was encoded in theta burst inputs. Therefore, non-spatial information may serve the function of a band-pass filter that modulates or otherwise influences spatial information in a GC. Spatial information with additional non-spatial information, rather than spatial information alone, is delivered downstream of the CA3 and CA1 in the hippocampus. The combined information in the theta wave is

transported to the CA3 and CA1 and processed at these regions. It is considered that memory is formed via theta oscillation in the CA3 and CA1 (Pignatelli et al. 2012; Wagatsuma and Yamaguchi 2007). Thus, spatial information modulated with non-spatial information tends to be stored in hippocampal memory. This is in agreement with a report that non-spatial information enhances hippocampus-dependent memory of spatial information (Rasch et al. 2007). We conjecture that the DG serves as a firewall for the hippocampus and selectively lets information through to acquire refined memory.

Spatial information can induce GC activation, even in the absence of non-spatial information in the case of strong synaptic weights of MPP, as shown in the case of input at around 8 Hz in Fig. 4d. Furthermore, the Hayashi–Nonaka GC model demonstrated that MPP synapses are selectively enhanced through long-term synaptic plasticity when non-spatial and spatial information is concurrently applied through the LPP and MPP, respectively (Hayashi and Nonaka 2011). However, for the firewall of a GC to operate properly, the synaptic weights of the MPP should be kept in a specific range where MPP inputs alone cannot effectively activate a GC, as shown in the bursting input pattern (2–4 pulses) in Fig. 5b, which corresponds to panel 3 in Fig. 4c. Therefore, it is highly likely that the synaptic weight of MPPs is kept in the range where inputs through both pathways are required to effectively co-activate GC, as shown in Fig. 5c and d. In this particular case, the results may support the idea that in wild rats, spatial information modulated with non-spatial information is more useful than spatial information alone. Spatial information combined with non-spatial information can represent various types of spatial information, such as places with food or places with predators. Thus, hippocampal memory composed of spatial information modulated with non-spatial information has advantages for surviving. If certain spatial information always involves non-spatial information, GC activation evoked by spatial information alone through long-term synaptic plasticity may not affect survival. However, it may reduce the chance of survival if any spatial information activates GC regardless of the presence of non-spatial information.

Ishizuka et al. (2004) showed that the inhibitory inputs through GABA_A receptors are required for the theta-band-pass filter. Under inhibitory conditions, high-frequency inputs (>20 Hz) suppress the activity of a GC. In this study, we showed that DDs induce EPSP depression in the presence of inhibition (the absence of picrotoxin) when a 20-Hz random pulse input was applied. Although in their study DDs and MDs were not distinguished, these results indicate that high-frequency input (>20 Hz) induces EPSP depression at DDs and consequently suppresses GC activation. Therefore, MD input alone is not sufficient for GC activation. The synaptic weights of a DG are kept in the

range where simultaneous inputs to DDs and MDs are required for GC activation.

In the hippocampus, pathway-dependent short-term plasticity allows the firewall to select what spatial information is allowed to continue downstream. Previous studies proposed hippocampal models that acquire sequential memory from the inputs at regular theta intervals (Lisman 1999; Lisman et al. 2005; Yamaguchi 2003). Synaptic plasticity in the hippocampus obeys the spike-timing-dependent plasticity (STDP) rule (Bi and Poo 1998; Debanne et al. 1998), thus regular-interval inputs within the time window of STDP are required in order to form a memory. Our results suggest that part of the spatial information encoded in regular burst inputs is filtered out, and inputs propagate downstream toward the hippocampus at irregular intervals outside the plasticity time window. Therefore, the hippocampus is equipped with mechanisms that enable the hippocampal network to acquire sequential memory on the assumption that inputs arrive irregularly. Further research is necessary in order to elucidate the mechanism of formation of hippocampal memory.

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