Phase dependency of long-term potentiation induction during the intermittent bursts of carbachol-induced β oscillation in rat hippocampal slices

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The rodent hippocampus possesses theta (θ) and beta (β) rhythms, which occur intermittently as bursts. Both rhythms are related to spatial memory processing in a novel environment. θ rhythm is related to spatial memory encoding process. β rhythm is related to the match/mismatch process. In the match/mismatch process, rodent hippocampus detects a representation matching sensory inputs of the current place among the retrieved internal representations of places. Long-term synaptic potentiation (LTP) is induced in both processes. The cholinergic agent carbachol induces intermittent θ and β oscillations in in vitro slices similar to in vivo bursts. LTP is facilitated during the generation of θ oscillation, suggesting that the facilitation of LTP is dependent upon the phases of intermittent burst (burst phases) of the oscillation. However, whether this is the case for β oscillation has not yet been studied. In the present study, LTP-inducing θ-burst stimulation was administered at the different burst phases of carbachol-induced β oscillations (CIBO), and the synaptic changes were measured at CA3-CA3 pyramidal cell synapses (CA3 synapse) and at CA3-CA1 pyramidal cell synapses (CA1 synapse). At the CA3 synapse, the largest magnitude of LTP was induced at the late burst phases of CIBO. At the CA1 synapse, LTP was induced only at the late burst phases. Modulation of LTP was suppressed when CIBO was blocked by the application of atropine at both synapses. The results suggest that the bursts of hippocampal β rhythm can determine the optimal temporal period for completing with the match/mismatch process.

Key words: hippocampus, β rhythm, novelty, match/mismatch process, learning

Rodents have theta (θ, 4–8 Hz)¹ and beta (β, 12–35 Hz)² rhythms associated with the development of spatial memories. When a rodent is placed in a novel environment and begins to explore, hippocampal θ rhythm is induced initially, followed by β rhythm². β rhythm is induced independently with the generation of θ rhythm and both rhythms appear intermittently as bursts in a wax-and-waning fashion. θ rhythm is thought to be related to spatial memory encoding and retrieval, and β rhythm is thought to be related to the match/mismatch process in novelty detection. In the match/mismatch process, the hippocampus discards mismatched place representations and identifies matching representations among those retrieved by incoming sensory inputs of the current place when a rodent revisits a previously experienced place¹. After the matching, the matched representations are reconsolidated. Memory encoding and matching processes require synaptic plasticity³,⁴. β rhythm is also related to the retrieval process in odor discrimination learning⁵ and is important in long-range synchronization of cognitive processes⁶.

Long-term synaptic potentiation (LTP) is the foremost
example of synaptic plasticity as the basis of memory processing and formation. While LTP is observed in in vivo θ rhythm\(^9\), it has not yet been examined in β rhythm. The cholinergic agent carbachol induces θ oscillation in rat hippocampal slices\(^{10}\), which is similar to in vivo θ rhythm; in both cases, the oscillation occurs intermittently as bursts\(^{11}\). Natsume and Kometani\(^{12}\) studied the effect of θ oscillation generation on LTP and found that the magnitude of LTP is modulated by the timing of the stimulus delivered during the intermittent burst interval. LTP is facilitated when it is induced during θ rhythm\(^{12}\), suggesting that spatial memory encoding and retrieval will occur during the generation of θ rhythm.

Hippocampus CA3 pyramidal cells have inputs from the dentate gyrus and entorhinal cortex, as well as from other CA3 pyramidal cells. CA1 pyramidal cells have inputs from the entorhinal cortex and CA3 pyramidal cells via Schaffer collaterals\(^{13}\). LTP is induced at CA3-CA3 pyramidal cell synapses (CA3 synapse) and at CA3 Schaffer collateral and CA1 pyramidal cell synapses (CA1 synapse)\(^{14}\). The hippocampal CA3 region has been proposed to play a role in encoding memories and in the retrieval of encoded representations\(^{15}\). The hippocampal CA1 region has been proposed to be involved in the match/mismatch process\(^{7,8}\) by comparing the retrieved representations from the CA3 region with afferent sensory inputs from the entorhinal cortex, and identifies matched representations associated with the sensory inputs.

Carbachol-induced β oscillation (CIBO) in rat hippocampal slices\(^{16,17}\) is a model for in vivo β rhythm\(^2\). CIBO occurs in CA3 and CA1 regions intermittently as bursts. The relationship between the induction of LTP and β rhythm has not yet been established. The magnitude of LTP may be modulated at the different timing of the LTP-inducing stimulus delivered during the intermittent burst interval of CIBO, similar to what is seen in carbachol-induced θ oscillation. Note that there are two kinds of periodic events in this phenomenon: one is the β oscillation and the other is the intermittent burst of β oscillation. Here, the “burst phase” is defined as the phase of the intermittent bursts of CIBO, and it is different from the phase of β oscillation. In the present study, 0-burst stimulation (TBS), an LTP-inducing stimulus, was given at the various burst phases of CIBO at CA3 and CA1 synapses to clarify whether the magnitude of LTP was modulated or not when CIBO was induced in a hippocampal slice.

Materials and Methods

The present data were obtained from 300 hippocampal slices (450-μm thick) of 165 male Wistar rats aged 3–5 weeks. The experiments were carried out in compliance with the Guide for the Care and Use of Laboratory Animals at the Graduate School of Life Science and System Engineering of Kyushu Institute of Technology. Rats were anesthetized by diethyl ether and decapitated. The brains were rapidly removed and placed into oxygenated cold (0°C) artificial cerebrospinal fluid (ACSF). The composition of ACSF was as follows (in mM): 124 NaCl, 5 KCl, 1.25 NaHPO\(_4\), 2 MgSO\(_4\), 26 NaHCO\(_3\), 10 glucose, and 2 CaCl\(_2\). The hippocampus was dissected free and transverse slices were obtained using a tissue slicer (Micro Slicer Zero-1, Dosaka-EM Co., Japan). Experimental procedures began after incubation in a holding chamber at room temperature for more than 1 hour.

The cholinergic agent carbachol induces CIBO intermittently in hippocampal slices\(^{16}\). The recording electrode (2 M NaCl, <2 MΩ) was placed in the stratum pyramidale in CA3 or CA1 subregions to record the CIBO. The field potential of CIBO from the glass microelectrode was amplified (×1000), band-pass filtered between 1 Hz and 0.3 kHz using an extracellular amplifier (ER-1, Cygnus Technology, USA), and sampled on a PC with 1 kHz using pClamp 10.0 software (Molecular Devices Co., USA).

The bursts of CIBO were induced with the application of 30 μM carbachol as shown in Figure 1. They achieved steady state approximately 15 min after the application began. The averaged frequency, amplitude, duration and inter-burst interval were measured in the steady state. The frequency of CIBO within an individual burst reached a steady state 2 s after the onset of the burst. Frequency was measured by fast Fourier transform (FFT) analysis for 1 s in the steady state. The analysis was calculated using pClamp 10.0. The duration represents the time that the burst of CIBO was maintained (Fig. 2A). The averaged peak-to-peak amplitude was measured for the same time period for frequency. The inter-burst interval (IBI) was measured as the time between the end of one burst and the start of the next (Fig. 2A). The bursts of CIBO are simultaneously observed at CA3 and CA1\(^{16}\).
CA3 and CA1 LTP experiments were done. In the CA3 experiment, concentric bipolar stimulation electrodes with external diameters of 300 μm (FHC Inc., USA) were placed in the stratum radiatum to stimulate associational fibers of CA3 pyramidal neurons antidromically; a recording electrode was placed in the stratum radiatum to record the population excitatory postsynaptic potential (pEPSP) at the CA3-CA3 pyramidal cell synapses (called CA3 synapse). In the CA1 LTP experiment, the stimulation electrode was put in the stratum radiatum of CA1 to stimulate Schaffer collaterals orthodromically. The recording electrode was placed in the stratum radiatum to record the population excitatory postsynaptic potential (pEPSP) at the CA3-CA1 pyramidal cell synapses (called CA1 synapse). The pEPSP was amplified (×1000), band-pass filtered between 1 Hz and 3 kHz using the extracellular amplifier ER-1 (Cygnus Technology), and sampled on a PC with 10 kHz using pClamp software.

A 100-μs rectangular test pulse was emitted 3 times at 30-s intervals around 1 min before TBS, and 3 times at the same interval around 10, 20, and 40 min after TBS to measure the effect of TBS on pEPSP slopes. Test pulses were given at the burst phase of 60° (Fig. 2B; defined below) of CIBO. The pEPSP slope was calculated from each pEPSP, and the averaged slope among three pEPSPs was plotted at each time point (for example, the figures on the right in Fig. 4). The test pulse began 20 min after the onset of carbachol application. Stimulation intensity of the pulse was adjusted before the application of carbachol so that the amplitude of pEPSP was two-thirds of the maximum amplitude. The stimulation intensity of TBS was also set to the same as that of the test pulse. To validate the induction of LTP, pEPSP was analyzed by measuring its initial slope, which contained only an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-dependent fast pEPSP component. The slope was calculated by the least squared method using pClamp. The relative pEPSP slope was defined as that normalized by the averaged pEPSP slope at 1 min before TBS. The relative pEPSP slopes at 40 min were statistically compared with those at 1 min before TBS, and the significant difference probability was calculated to determine whether LTP was induced or not. The magnitude of LTP was defined as the relative pEPSP slope at 40 min after TBS. TBS, which consisted of 5 bursts of five 10-ms interval pulses with 200-ms intervals, was applied. TBS was administered during a burst of CIBO, just after the termination of the CIBO burst, during the rest of the CIBO burst, and just before the onset of the CIBO burst. For the sake of convenience, these TBS stimulus timings are defined as the burst phases of 0°, 60°, 180°, and 330°, respectively (Fig. 2B). At 2 s from the onset of CIBO, the frequency reached a steady state as described before, and the burst phase of 0° is defined as 2 s after the onset of a burst of CIBO. The burst phase of 360° is defined as 2 s after the onset of the next burst of CIBO. The interval between 0° and 360° was divided proportionally, and the phases 60°, 180°, and 330° were determined (Fig. 2B). Note again that the “burst phases” are different from the phases determined during periodic β oscillation.

Atropine sulfate (muscarinic acetylcholine receptor antagonist; atropine) was applied to determine whether CIBO modulates synaptic plasticity or not. In the pharmacological experiments, atropine was administered 20 min after the application onset of carbachol and LTP was induced 30 min later.

All drugs were purchased from Sigma (USA). Data are expressed as mean±SEM (standard error of the mean). Statistical significance was set at p<0.05.

Results

Induction of CIBO

Hippocampal slices had no spontaneous activity at CA3 and CA1 before the application of carbachol (Fig. 1, top). After the application of carbachol, CIBOs were induced at both regions. The bursts of CIBO occurred simultaneously at CA3 and CA1 as reported previously10. The frequency of CIBO was 15.1±0.7 Hz, IBI was 24.9±2.7 s, duration was 6.8±0.2 s, and amplitude was 4.5±0.6 mV (n=6).

pEPSP recorded in CIBO

With the application of carbachol, the mono-phase negative deflection that reflects pEPSP sometimes includes positive deflections reflecting population spikes at CA3 and CA1 synapses. The pEPSPs at both synapses are shown in Figure 3. To identify pEPSPs, 10 μM of the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) was applied, and pEPSPs were suppressed (Fig. 3). Similar results were observed in 3 slices. The field potential from 2 to 15 ms after the onset of the stimulation is defined as the duration of pEPSP.
The time course of pEPSP without TBS recorded in CIBO

The slope of pEPSP was calculated between 3 and 10 ms after the onset of stimulation. The slope at the CA3 synapse was \(-0.72\pm0.14\) mV/ms (n=10) and the slope at the CA1 synapse was \(-2.7\pm0.34\) mV/ms (n=10) before the application of carbachol. The application of carbachol decreased the slopes as previously reported \(^{15,16}\). The pEPSP slopes after the application were normalized with those averaged for 1 min before it. The normalized pEPSP slopes were 0.34\pm0.06 (n=5) at the CA3 synapse, and were 0.36\pm0.05 (n=5) at the CA1 synapse 20 min after the application. The decrease was significant at both synapses (paired \(t\)-test; \(p<0.05\)).

pEPSPs were recorded with test pulses for 41 min every 10 min without TBS, as in the LTP experiment protocol. The relative pEPSP slope at the CA3 synapse at the last 1 min to that at the first 1 min was 0.86\pm0.06 (n=3), and that at the CA1 synapse was 0.81\pm0.13 (n=3). They were not significantly different (paired \(t\)-test with those at the first 1 min; \(p>0.05\); n=3 at each synapse). Thus, the slope did not change significantly during the period of the LTP experiment.

Synaptic plasticity induced with TBS at different burst phases of CIBO

When TBS was administered at the 0° burst phase, the relative pEPSP slope significantly increased and was maintained for at least 40 min at the CA3 synapse (Fig. 4A). Thus, LTP was induced (Mann-Whitney U test compared with the relative pEPSP slopes before TBS, \(p<0.01\)). At the CA1 synapse, TBS increased the pEPSP slope just after the stimulation. Subsequently, the slope decreased. TBS did not have a long-term effect and induced short-term potentiation (Fig. 4A; one-way repeated measures ANOVA with Bonferroni’s post-hoc test, \(p<0.01\)). TBS at the 60° burst phase at the CA3 synapse induced LTD (Fig. 4B; Mann-Whitney U test, \(p<0.05\)). TBS did not significantly induce LTP or LTD at the same burst phases at the CA1 synapse. When TBS was administered at the 180° burst phase, LTP was induced at both the CA3 and CA1 synapses (Fig. 4C). The magnitudes of LTD at both synapses were significantly different from baseline (Mann-Whitney U test; \(p<0.01\)). When TBS was administered at the 330° burst phase, LTPs were also induced at both the CA3 and CA1 synapses (Fig. 4D). The magnitudes of LTP at both synapses were significantly increased (Mann-Whitney U test; \(p<0.01\)).

Figure 5 (top) summarizes TBS-induced LTP at all burst phases of CIBO at the CA3 synapse. The magnitudes of LTP at all phases were significantly different from baseline. The magnitudes at the late burst phases were larger than those at the earlier phases. At the CA1 synapse, TBS induced significant LTP only at the later burst phases of 180° and 330° of CIBO (Fig. 5, bottom). In contrast to what is seen in carbachol-induced \(\theta\) oscillation, in \(\beta\) oscillation, the magnitude of LTP at the rest phase of the oscillation is facilitated at the CA3 synapse and LTP is induced at the CA1 synapse.

Pharmacological experiment of the synaptic plasticity study

CIBO is sensitive to atropine, as has been previously reported \(^{16,17}\). Atropine suppressed CIBO in CA3 and CA1 synapses, and induced individual field activities (IFA) \(^{16}\) in both regions (Fig. 6). The induction of LTP was investigated during the generation of IFA. The protocol to induce LTP was identical to that described previously, except that TBS was not administered at the specific burst phase shown in Figure 5 because the application of atropine had suppressed the CIBO bursts, and the burst phase was not determined.
While we attempted to induce synaptic change by TBS at the CA3 and CA1 synapses in 3 hippocampal slices, LTP was induced in neither region (Fig. 6). The magnitude of LTP at the CA3 and CA1 synapses were 1.08 ± 0.06 (n = 3) and 0.95 ± 0.04 (n = 3), respectively (Fig. 6A and B). They were not significantly different from respective baselines. LTP was not induced with TBS under the suppression of the CIBO burst. However, there is a possibility that the maximum pEPSP slope changes with the application of atropine; thus, there would be less room for the detection of an increase in the pEPSP slope. Therefore, the maximum pEPSP slope was measured before TBS application. The ratio of the test pEPSP slope to the maximum slope was calculated. The ratios were 37 ± 7% (n = 3) and 34 ± 5% (n = 3) at the CA3 and CA1 synapses, respectively. Thus, there was adequate room for the pEPSP slope to be increased by TBS and the possibility was ruled out.

**Dependence of the relative pEPSP slope on the burst phases of CIBO**

pEPSP is dependent upon the phase of the θ rhythm. There is a possibility that pEPSP changes with the burst phases of CIBO, and that these changes lead to different magnitudes of LTP with TBS at different burst phases, as shown in Figures 4 and 5. In the LTP experiment, TBS was administered at the different burst phases of CIBO. TBS consisted of 5 bursts of 5 pulses. Figure 7 illustrates the relative pEPSP slopes, with the first stimulation pulse in TBS plotted with the burst phases. The relative pEPSP slopes at the CA3 and CA1 synapses were not significantly dependent upon the burst phases of CIBO (Fig. 7; one-way repeated measures ANOVA; n = 3 each at the CA3 and CA1 synapses; p > 0.05). The correlation between the relative slope of the first pEPSP in TBS and the magnitude of LTP was analyzed. The Spearman’s rank correlation coefficients at the CA3 and CA1 synapses in CIBO were 0.049 and
There was no significance in any correlation (significant test for Spearman’s rank correlation coefficient; \(n = 22\) and 16 at the CA3 and CA1 synapses in CIBO). Thus, the increases in the magnitude of LTP at the CA3 synapse and the induction of LTP at the CA1 synapse at the late burst phases of 180° and 330° were not dependent upon the degree of the excitatory postsynaptic potential.

**Discussion**

TBS was administered at several burst phases of CIBO at hippocampal CA3 and CA1 synapses. LTP was induced at all of the burst phases at the CA3 synapse, and the magnitude of LTP increased at the late burst phases of CIBO (Figs. 4 and 5). At the CA1 synapse, on the other hand, LTP was induced only at the late burst phases, while LTP was not induced at the earlier phases (Figs. 4 and 5). The modulation of the magnitude of LTP at both synapses was suppressed with the suppression of CIBO (Fig. 6). It was not due to a floor effect enabling the pEPSP slope to be changed by decreasing the maximal slope. CIBO is a model for in vivo \(\beta\) rhythm, which occurs intermittently as bursts in a wax-and-wane fashion. The results from the present study suggest that 1) the generation of \(\beta\) rhythm in vivo can modulate the synaptic plasticity at both CA3 and CA1 synapses temporally; 2) the magnitude of LTP will be facilitated at the second half of the interval of the bursts of \(\beta\) rhythm at the CA3 synapse; and 3) there is a time window for the induction of LTP at the second half of the interval of the bursts of \(\beta\) rhythm at the CA1 synapse. With these data, the dependence of LTP induction on the burst phases of CIBO is demonstrated for the first time.

Carbachol activates muscarinic and nicotinic acetylcholine receptors. The induction of CIBO requires the activation of muscarinic acetylcholine receptors, whereas it does not require the activation of nicotinic acetylcholine receptors. The magnitude of LTP was modulated in the inter-burst interval of CIBO (Fig. 5). Hence, the dependence of LTP induction on the burst phases of CIBO will not require the activation of nicotinic receptors.

The magnitude of LTP at the CA3 and CA1 synapses was increased at the late burst phases of CIBO (Figs. 4 and 5). Because the magnitude of LTP is dependent on excitatory synaptic transmission, the pEPSP slopes were measured at the different burst phases. The slopes did not vary according to phase (Fig. 7). In the case of carbachol-induced \(\theta\) oscillation, the least feedback inhibition occurs during the oscillation. Feedback inhibition to the CA3 and CA1 pyramidal cells is mediated by GABA transmission and the blockade of GABA transmission facilitates LTP. Thus, the decrease in GABA transmission during the \(\theta\) oscillation can increase the magnitude of LTP. The increases in the magnitude of LTP at the late burst phases in the present study were not caused by excitatory synaptic transmission; they may have been caused by the disinhibition at the burst phases in CIBO, as is seen in the \(\theta\) oscillation. In the inter-burst interval, GABA transmission can be modulated, and this modulation can cause a change in the magnitude of LTP.

LTP is facilitated to a greater degree when it is induced at the late burst phases, at the rest of CIBO (Figs. 4 and 5). It is facilitated, on the other hand, when it is induced during the generation of carbachol-induced \(\theta\) oscillation. The modulation of the magnitude of LTP during the intermittent burst interval of \(\theta\) oscillation is different from that of \(\beta\) oscillation. The modulation can be dependent on the burst frequency. In vitro CIBO and \(\theta\) oscillation are models for in vivo \(\beta\) and \(\theta\) rhythm, respectively. The difference of the two in vivo rhythms is not only the frequency, but also the induction time window for LTP relative to the onset of the burst of the rhythm.

Both hippocampal \(\theta\) and \(\beta\) rhythms are induced when a rodent processes spatial information in a novel environment. When the rodent is placed in a novel environment and begins to explore, hippocampal \(\theta\) rhythm is induced. Initially, \(\beta\) rhythm is not observed; \(\beta\) rhythm is induced when the rodent revisits a place it experienced before. Hippocampal \(\theta\) rhythm is thought to be related to spatial memory.
encoding and retrieval of the stored representation. β rhythm is thought to contribute to cued recall by comparing internal representations with incoming sensory inputs and finding a matching representation of the inputs. When a rodent is first placed into a novel environment, sensory inputs indicating place information from the entorhinal cortex are encoded in the recurrent connections of hippocampal CA3 pyramidal cells. While the rodent is exploring the environment, it encodes incoming inputs as new representations of the places, one by one. Subsequently, when the rodent revisits the same place as before, the hippocampal CA1 network compares the stored representation retrieved in CA3 with the sensory inputs of the current place, and engages in the match/mismatch process. In the process, the CA1 region discards the mismatched representation until it finds a proper representation matching the current position of the rodent. When the CA1 region engages in the match process, induction of LTP at the CA1 synapse is necessary to build an association between the matched representation with the current sensory inputs. The results of this study show that the time window for LTP induction at the CA1 synapse would be determined by the burst of β rhythm. Thus, there will be a temporal relationship between the hippocampal match process and the generation of β rhythm in spatial processing. The timing of matching the retrieved representation may be determined by the bursts of β rhythm. During the generation of CIBO, on the other hand, LTP was not induced. Managing the mismatch representations does not require LTP. Thus, during β rhythm, the mismatch process may be completed. The in vivo inter-burst intervals of β rhythm fluctuate different from the in vitro CIBO model. The different duration for the match and mismatch process in case of in vivo may reflect the fluctuation of the interval. When the CA1 region detects a mismatched representation, it sends a signal that resets the retrieving representation to the CA3 region, prompting it to induce another representation and send it back to the CA1 region.
The hippocampal CA3 region is crucial for memory encoding and retrieval. It retrieves stored representations and sends them to the CA1 region during the match/mismatch process. In spatial processing, the CA3 network recalls the representation of a place that the rodent previously experienced, and has it propagate to the CA1 region; when the representation matches with the sensory input in CA1 region, and the representation accompanies memory reconsolidation. This reconsolidation accompanies synaptic plasticity. As discussed above, the match process is completed relative to the bursts of $\beta$ rhythm in the CA1 region. As evidenced by the present results, at the CA3 synapse, the largest magnitude of LTP was temporally related to the bursts of $\beta$ rhythm in the CA1 region. As evidenced by the present results, at the CA3 synapse, the largest magnitude of LTP was temporally related to match process. It is consistent that LTP is facilitated in the match process to reconsolidate the matched representation of the current place in the CA3 region. The long-range synchronization of $\beta$ rhythm between the CA3 and CA1 regions may be necessary for perfecting the timing between representation retrieval in the CA3 region and the match/mismatch process in the CA1 region.

Conclusion

Hippocampal $\beta$ rhythm occurs intermittently as bursts. LTP is induced at various burst phases of CIBO at the CA3 and CA1 synapses. At the CA3 synapse, LTP was induced at all burst phases and the magnitude of LTP increased at the late burst phases of CIBO. At the CA1 synapse, LTP was induced only during at the late burst phases. The modulation of LTP was disrupted at both synapses when CIBO was blocked. These results suggest that the intermittent bursts of $\beta$ rhythm may determine the temporal period for synaptic change at the CA3 and CA1 subregions in the hippocampal neuronal network. These results may reflect the coordinated memory processes of the CA3 and CA1 regions for stored representation retrieval and the match/mismatch process.

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