Title:

Spike timing dependent LTP and LTD in the CA1 area of hippocampal slices by the optical imaging

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ABSTRACT

Spike timing dependent long-term potentiation (LTP) / depression (LTD) were investigated in the CA1 area of hippocampal slices by the

optical imaging. A pair of electrical pulse stimuli was used to stimulate the schaffer commissural collateral and the stratum oriens with various sets of the relative timing (τ) between the two stimuli . The induction of LTP / LTD were closely related to the timing τ . The profile of LTP and LTD for the timing τ were classified into two types depending on the layer specific location along the dendrite. One was a symmetric time window observed in the proximal region of stratum radiatum (SR) and the other was an asymmetric one in the distal region of SR. These results were discussed in the relation to memory functions ; CA1 network structures and learning rules.

1. INTRODUCTION

LTP and LTD have generally considered to be cellular basis of learning and memory. Since Bliss and Lømo (1973) firstly found in the hippocampal CA1 that the electrical high frequency stimulus “tetanus” (100 - 500 Hz) effectively produce LTP, frequency dependent LTP in broad range (2 - 500 Hz) and temporal pattern dependent LTP have been reported (Lynch et al., 1989 ; Tsukada et al., 1994, 1996 ; Aihara et al., 1997, 2000). On the other hand, LTP induced by co-activity between pre- and post-neurons (Hebb type) had been investigated (Magee and Johnston, 1997 ; Bi and Poo, 1998 ; Nishiyama et al., 2000). Bi and Poo found an asymmetric profile of LTP and LTD for the relative timing τ between pre- and post-neurons in cultured hippocampal neurons.

In this paper, the spike timing dependent LTP and LTD were investigated

in the CA1 area of rat hippocampal slice, by using a pair of electrical pulse stimuli to schaffer commissural collaterals (SC) and stratum oriens (SO). We compared the profile of LTP and LTD for τ in a slice with that in cultured neurons, and discussed about information processing of hippocampal CA1 networks.

2. MATERIALS AND METHODS

2.1 General method

The experiments were performed on hippocampal slices, 400 μm thickness, taken from female wistar rat 4 weeks. The tissue was sliced at an angle of 30 – 45 ° to the long axis of the hippocampus. This angle was selected because the plane was parallel to the alvear fibers that were on the surface of the tissue and the trisynaptic circuit. The slices maintained at 31℃ in an experimental submarge chamber with a normal medium, artificial cerebrospinal fluid (142mM NaCl, 5.0mM KCl, 2.6mM NaH_2PO_4, 2.0mM $MgSO_4$, 2.0mM $CaCl_2$, 26mM $NaHCO_3$, 10mM glucose). Positions of a pair of stimulus electrodes are shown in fig.1. One bipolar tungsten electrode was placed at a fixed position in stratum radiatum of the specific region to stimulate the SC of CA3 (fig.1, Stim.A). The other bipolar electrode was placed at a fixed position in the stratum oriens (Fig.1, Stim.B). The optical recording area was depicted by the solid square (Fig.1) of which the left side was fixed at the boundary between CA2 and CA1.

2.2 Stimulation

The intensity of electric pulse to stimulate the SC (Stim.A) and SO (Stim.B) was fixed at a constant value. Exactly it was half intensity to produce the maximum population in CA1 region (0.1 – 0.5 mA). The duration of a stimulus pulse, total number of pulses and inter-stimulus interval (ISI) were fixed at 0.2 ms, 200 pulses and 2 s, respectively. The stimulus condition, ISI = 2 s, induced no LTP and LTD (Aihara et al., 1998). A pair of pulse stimuli was used to stimulate the SC (Stim.A) and SO (Stim.B) with various sets of the relative timing ($\tau = t_A - t_B$), where the

clock time of Stim.A (t_A) was a reference stimulus against that of Stim.B (t_B). The τ were 0, ±5, ±10, ±20, ±50 ms and various sets of (0, τ) were (0, -50), (0, -20), (0, -10), (0, -5), (0, 0), (0, 5), (0, 10), (0, 20), (0,50) seen in Fig.2.

2.3 Optical imaging

In the optical imaging , slices were stained for 40 min with 0.1 mg/ml RH482 in normal medium and then were washed away and recovered for an additional 10 min. A naive slice was used for each stimulus sequence of control- paired stimulus- test. Slices were viewed with 5×objective. The voltage-sensitive dye signals were recorded with 700±30 nm interference filter. The transmitted light was detected by a 128×128square array of photodiodes; each has 1.7×1.7 mm receptive area. Each photodiode received light from 14×14 μm area of the microscope objective field, and was coupled to current-to-voltage converter and amplifier (gain; 2000); we used the HR Deltaron 1700 system (Fujifilm microdevices Co.). This has an adequate resolution in space (14×14 μm / single photopixel) and in time (0.6 ms / single frame) to analyze spatio-temporal activities of the CA1 neural network. At the beginning of each experiment, the “test stimulus” (TS, at Stim.A site, single pulse) was applied once every 20 s (0.05 Hz) for more than 20 min to ensure that the amplitude of the population spike was stable. Thereafter, one of the paired stimuli with (0, τ) was delivered as a “conditioning stimulus (CS) ”. After giving the CS, the same TSs were given every 20 s to estimate the change in responsiveness induced by CS. In the experiment, 16 responses were averaged to improve the signal to noise ratio for both unconditioned and conditioned (15 - 25 min after the CS) TS responses. The magnitude of

LTP/LTD was estimated by mean percentage changes of the population spikes of 5×5 pixels in hippocampal CA1 slice (conditioned TS–response / unconditioned TS–response) (Fig.3). A new slice was used for for each stimulus sequence of TS/CS/TS. Seven slices were used for each paired stimulus. All values were expressed as the mean±SE (%) and results were analyzed for significance ($p < 0.05$) by ANOVA .

3. RESULTS

1. Spike timing dependent LTP/LTD

We show that the timing factor between pre- and post-neurons is very important to induce LTP and LTD. Fig. 4A is the optical imaging results of LTP and LTD induced by a series of different spike timing τ . The widest and strongest LTP was observed when the simultaneous stimuli ($\tau = 0$ ms) were given. LTP decreased rapidly in space and time as the absolute value of relative timing τ increased in side of 121=15ms. Acordingly, LTP was induced when back propagating spikes (Stim. B) peaked within a time window of 15 ms before and after the onset of Stim.. A. Whereas LTD was induced in both side at $|\tau| = 20$ ms (Fig.4(A-d), (A-h)) and outside the 50 ms time window, synaptic modification was absence (Fig.4 (A-e), (A-i)). From these results, LTP and LTD globally showed a symmetric window of a so-called “Mexican hat function” for the spike timing τ .

To examine the effect of the GABAergic inhibitory interneurons on LTP/LTD, we applied bicuculline (25 μ M, GABA receptor antagonist) to the hippocampal slices and repeated the same experiments using the same protocol of the relative timing τ . Fig.4B showed the optical imaging data with bicuculline application. We compared two spatial distributions

with bicuculline(Fig. 4B) and without bicuculline (Fig. 4A). The two spatial distributions of LTP for τ =0 were almost the same as seen in Fig. 4B-a and 4A-a. One side of LTD for τ =20 ms (Fig. 4a-D) was clearly blocked by bicuculline as seen in Fig. 4B-d and the other side of LTD for τ =-20 ms (Fig. 4A-h) was little affected by bicuculline as seen in Fig. 4B-h. The profile of LTP/LTD in the slice with bicuculline showed an asymmetric window for the spike timing τ .The same tendency was observed in seven pair of slices. The LTD for τ =20 ms is closely related to the GABA ergic inhibitory connections in the hippocampal CA1 networks.

To further examine the location dependence of synaptic modification along the dendritic trees, we calculated for the layer-specific location from proximal to distal in stratum radiatum (SR) (Fig.5). The symmetric window was found on the specific location; the proximal region of SR where GABAergic interneurons project on, while the asymmetric window was found on the distal region of SR where GABAergic interneurons don't project on. The protile of LTP/LTD in the proximal region in slices with bicuculline showed the asymmetric one (Fig.6), which is similar to that in cultured hippocampal neurons (Bi and Poo,1998). The one side of LTD at τ =20ms was blocked (astarisk in Fig.6). From these results ,the one side of LTD at τ =20ms depends on the GABAergic inhibitory interneurons in the CA1 area.

4. DISCUSSION

As a rule of synaptic modification, Hebb (1949) postulated an idea that the synaptic modification is strengthened only if the pre- and post-synaptic elements are activated simultaneously. Recently, a series of experiments have focused on the experimental evidence of Hebb's postulation. Stuart and Sakmann (1994) showed that the action potentials initiated at the axon hillock and propagated back into the dendritic tree. Markram et al. (1997) found to induce LTP and LTD by pairing EPSPs and back propagating spikes. These findings have been confirmed and extended by using pyramidal cell pairs in hippocampal cultures (Debanne et al., 1998 ; Bi and Poo, 1998). In each case, LTP and LTD were induced depending on the spike timing (τ) between the presynaptic and postsynaptic spiking. LTP was induced when postsynaptic spikes peaked within a window 20 ms after the onset of EPSPs. These dependence on temporal order have been understood by the following mechanism (Linden 1999). For the modulation of LTP, arrival of back propagating spike during the EPSP functions to depolarize the postsynaptic membrane strongly which activates the NMDA receptor and Ca^{2+} entry. In contrast, for that of LTD, when the spikes precede the EPSPs, the EPSPs coincidence with the after-hyperpolarization, which may dampen NMDA receptor mediated Ca^{2+} influx.

In our experiment in hippocampal slices, two types, symmetric and asymmetric time windows for the timing τ were found depending on the specific location along the dendritic trees in the hipocampal CA1 networks. The asymmetric profile was observed in the distal region of stratum radiatum (SR), which is similar to that in cultured hippocampal CA1 neurons, while the symmetric one was observed in the proximal region of

SR and has two distinct windows for the induction of LTD around $\tau = \pm$ 20 ms, which is similar to those report in the slice preparation (Nishiyama et al., 2000). The appearance of LTD window around τ = 20 ms result from the presence of inhibitory input in the slice preparation, because the LTD was blocked by bicuculline (GABA receptor antagonist). Some hippocampal GABAergic interneurons (axo-axonic cells (AAC), baslet cells (BC), bi-stratified cells (BSC) and horizontal cells (HC)) are known to be important for setting the spatio-temporal conditions for synaptic modification in hippocampal CA1 pyramidal neurons (Paulsen O. and Moser E.I., 1998). They contact the pyramidal neurons via feed-forward (AAC, BC, BSC) and feed-back circuits (BC, HC) and are classified into distinct classes according to their input-output projections. Bi-stratified cells (BC) among them project on the proximal region of dendritic compartments at SR of pyramidal cells in a feed-forward manner. On the other hand, the distal region of SR has no inhibitory projections. The LTD window around τ = 20 ms may result from the specific projection of inhibitory circuits on the proximal region of dendrite. The region-specific profiles of LTP/LTD depend on the network with or without the inhibitory projection on the layer SR. Two factors of “after hyperpolarization” of spikes and “region-specific projection of inhibitory interneurons”, which organize “lateral inhibition” for timing τ, serve to underlie “symmetric” profile for timing τ, while one factor of “after hyperpolarization” of spike serves to organize “asymmetric” one. ”Symmetric” one with a sharp window for τ works as a coincidence detector between the input of CA3 shaffer collaterals and the output of CA1 pyramidal cells. The time window corresponds to the time interval of a gamma cycle in the idea that sequence information is processed in a time scheme of several gamma cycles (local)

in a theta cycle (global) (Lisman et al., 1999). On the other hand, "asymmetric" one with a broad time window after $\tau = 0$ ms, is able to integrate sequence information ("temporal summention") or to code phase information. This difference between the distal region and the proximal region of SR was seen in the results of temporal pattern dependent LTP using optical imaging of CA1 area of hippocampal slices (Aihara et al., 1997; Aihara et al., 2002). The temporal pattern sensitivity of LTP is even higher in the distal region than in the proximal region . These results suggest an important function of memory processing depending on the synaptic localization on dendrites of CA1 pyramidal cells.

5. ACKNOWLEDGEMENT

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Figure legends

Fig.1 Schematic draw of the hippocampal slice showing stimulation and recording conditions. Stim.A was placed at a fixed position in the stratum radiatum of CA1 area to stimulate the schaffer collateral commissural of CA3 region. And Stim.B was settled on stratum oriens, which is the output layer of CA1, to initiate back propagating action potentials. Optical recording area (128×128 pixels) was 1.75mm×1.75mm. DG, dentate gyrus ; F,fimbria.

Fig.2 Stimulus pattern with spike timing (τ). The duration of stimulus pulses, total number and inter-stimulus interval were fixed at 0.2 ms, 200 pulses and 2 s, respectively.

Fig.3 . The measurement method of a spatial distribution of LTP/LTD in the optical imaging

(a); an image of hippocampal CA1 area. Stim.A and Stim..B show the paired stimulus positions (b); a spatial distribution of optical signals (fractional changes in light intensity) before a paired stimulus, (c); a spatial distribution of optical signals after a paired stimulus, (d); a spatial distribution of LTP/LTD plotted by the ratio (h_1/h_0) of the fractional change in light intensity (e) (f); optical signals h_0 and h_1 obtained by averaging 5 × 5 pixels at corresponding location of before and after stimulus respectively.

Fig.4. Comparison of a spatial distribution of LTP/LTD in naive slice(A) and that with bicuculline(B)

(A); naive slice. The widest and strongest LTP (a) was observed when simultaneous stimulation ($\tau = 0$ ms) was given and the narrow and week

LTPs (b)(f),(e)(g), when τ =±5, ±10 ms. Whereas LTDs (d) and (h) were induced when the values of τ were ±20 ms. The profile of LTP/LTD for τ globally showed a symmetric dependence.
(B); slice with bicuculline. In comparison with those of naive slice, LTD for τ =20 ms was clealy blocked by bicuculline (d). The others were about the same as those of (A).

Fig. 5 Layer specific profiles of LTP/LTD at proximal and distal locations in stratum radiatum along the dendrite in hippocampal CA1 area
A; an image of optical recording area in hippocampal CA1 area showing two stimulus positions and six recording sites.
B; a symmetric window of LTP/LTD of three recording sites at a distance of 60 μm(proximal in SR) from the cell body layer.
C; an asymmetric window of LTP/LTD of three recording sites at a distance of 300 μm(distal in SR) from the cellbody layer.
A piece of LTP/LTD data shows the mean±SE of 7 slices. SO; the stratum oriens. SP :the stratum pyramidale. SR : the stratum radiatum . SL-M; the stratum lacunosum-moleculare.
Fig.6. Comparison of LTP/LTD of naive slice and that with bicuculline in a fixed proximal region of SR.
▲; the results of naive slice. ◆; those with bicuculline(25 μM).
All values were expressed as the mean±SE (%) in 5×5 pixels of 7 slices and results were analyzed for significance ($p < 0.05$) by ANOVA . The significant difference was appeared at τ =20ms(*).
Fig. 7 . Schematic explanation of LTP/LTD based on Hebbian covariance learning rule. In the Hebb rule, synaptic modifications of both increasing and decreasing synaptic weight are assumed by following equation;

$$\Delta w = \sum_{t} x(t) \cdot y(t + \tau)$$

Where Δw ; synaptic weight, x(t) ; a propagating pre-synaptic potential, y(t) ; a propagating back potential and τ ; relative timing between two stimuli.

(A); LTP mechanism. When a back propagating spike arrives within a window of the depolarized post-synaptic potential (PSP) after the onset of EPSPs, $\Delta w > 0$ which coresponds to LTP.

(B); LTD mechanism. When EPSPs arrive within after-hyperpolarization of the spikes $\Delta w < 0$ which coresponds to LTD.

(C);LTD mechanism. When the spikes arrive within a window of hyperpolarized PSP after the onset of IPSPs $\Delta w < 0$.

Where

APs ; action potentials, EPSPs ;excitatory post-synaptic potentials,

AHP ; after-hyperpolarization,

IPSPs; inhibitory post-synaptic potentials.

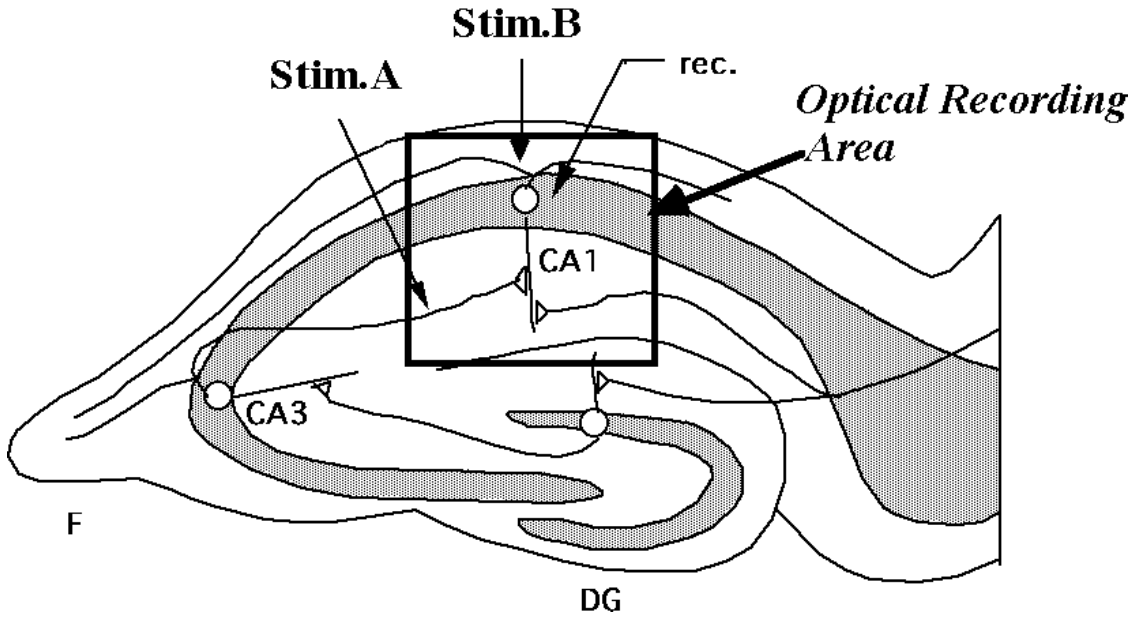

Fig. 1

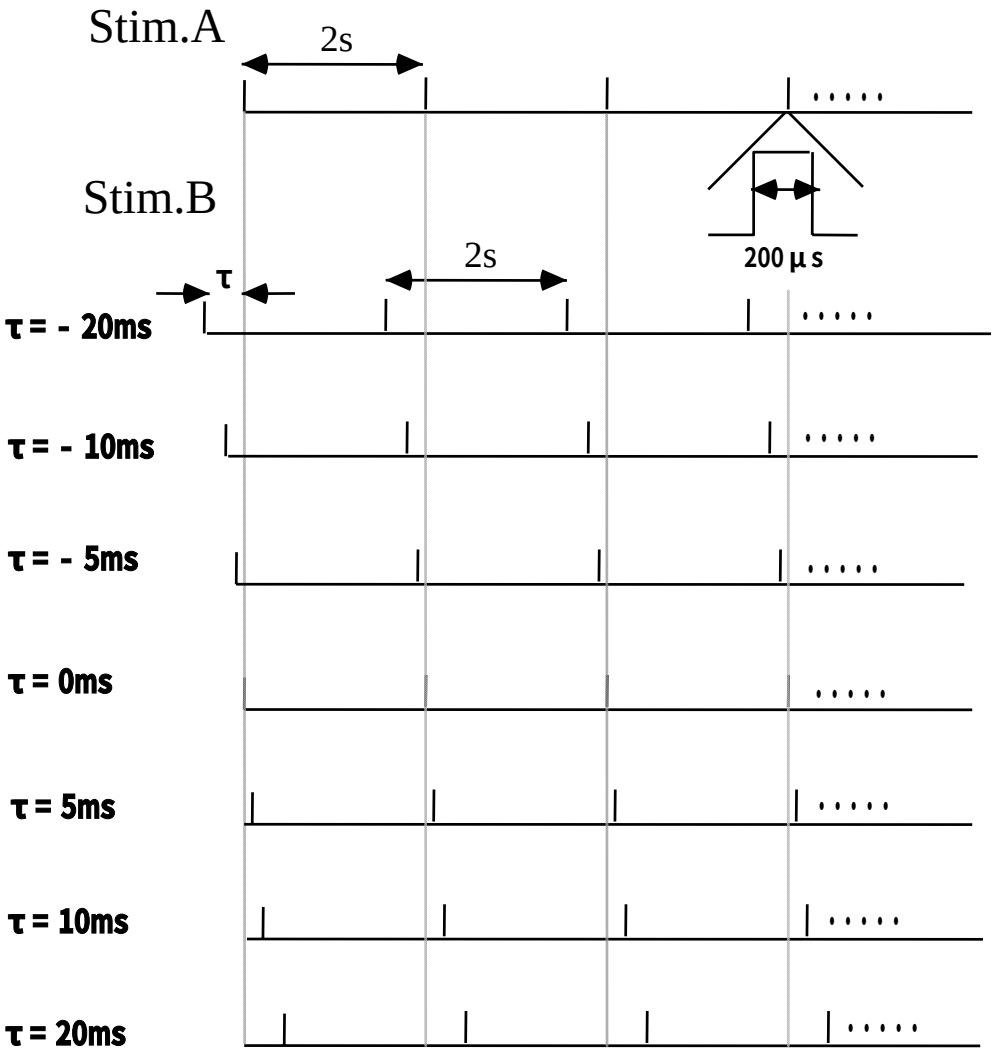
Stim.A
2s
Stim.B
200 µs
τ
2s
τ = - 20ms
τ = - 10ms
τ = - 5ms
τ = 0ms
τ = 5ms
τ = 10ms
τ = 20ms

Fig. 2

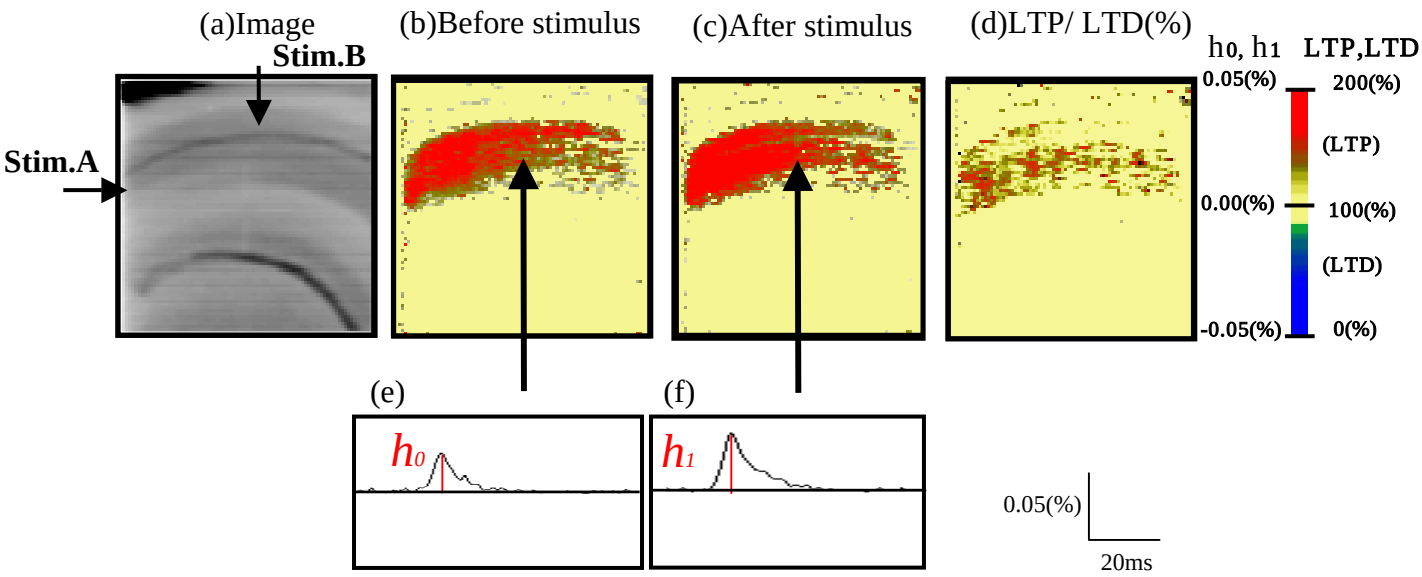
(a)Image
(b)Before stimulus
(c)After stimulus
(d)LTP/ LTD(%)
Stim.B
Stim.A
h0, h1
LTP,LTD
0.05(%)
200(%)
(LTP)
0.00(%)
100(%)
(LTD)
-0.05(%)
0(%)
(e)
(f)
h0
h1
0.05(%)
20ms

Fig. 3

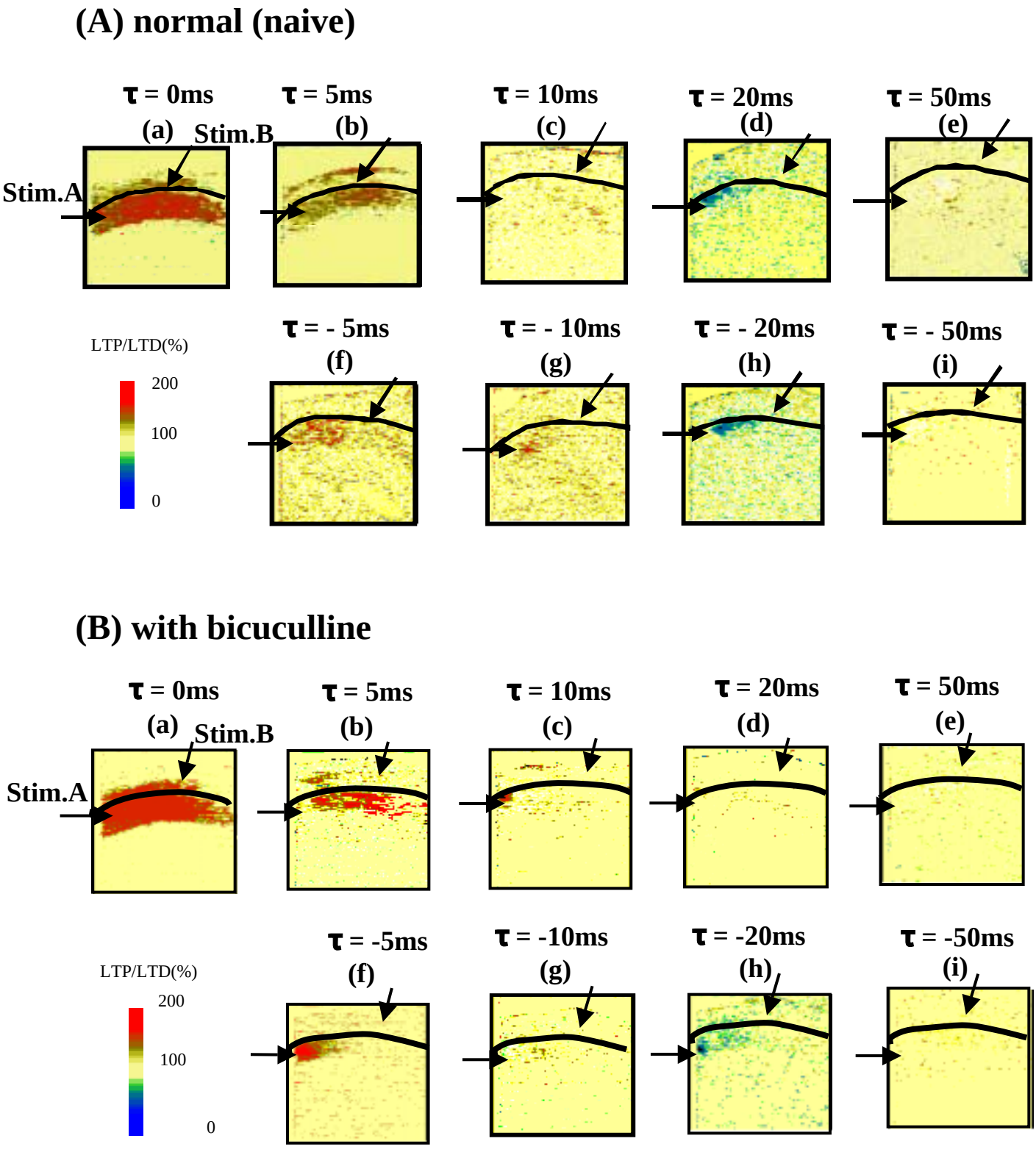
(A) normal (naive)
τ = 0ms
(a)
Stim.B
Stim.A
τ = 5ms
(b)
τ = 10ms
(c)
τ = 20ms
(d)
τ = 50ms
(e)
LTP/LTD(%)
200
100
0
τ = - 5ms
(f)
τ = - 10ms
(g)
τ = - 20ms
(h)
τ = - 50ms
(i)
(B) with bicuculline
τ = 0ms
(a)
Stim.B
Stim.A
τ = 5ms
(b)
τ = 10ms
(c)
τ = 20ms
(d)
τ = 50ms
(e)
LTP/LTD(%)
200
100
0
τ = -5ms
(f)
τ = -10ms
(g)
τ = -20ms
(h)
τ = -50ms
(i)

Fig. 4

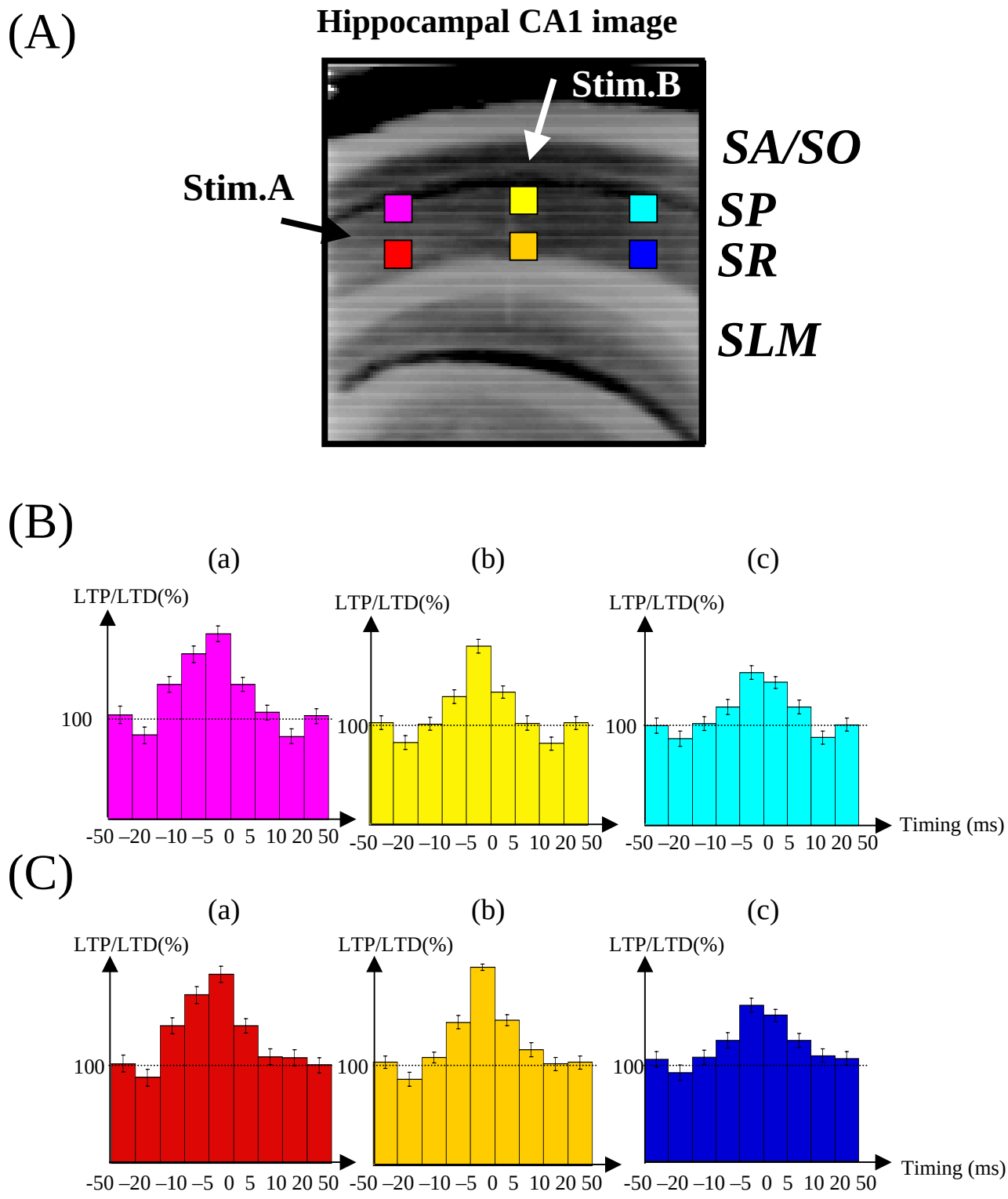
(A)
Hippocampal CA1 image
Stim.B
Stim.A
SA/SO
SP
SR
SLM
(B)
(a)
(b)
(c)
LTP/LTD(%)
100
-50 –20 –10 –5 0 5 10 20 50
Timing (ms)
(C)
(a)
(b)
(c)
LTP/LTD(%)
100
-50 –20 –10 –5 0 5 10 20 50
Timing (ms)

Fig. 5

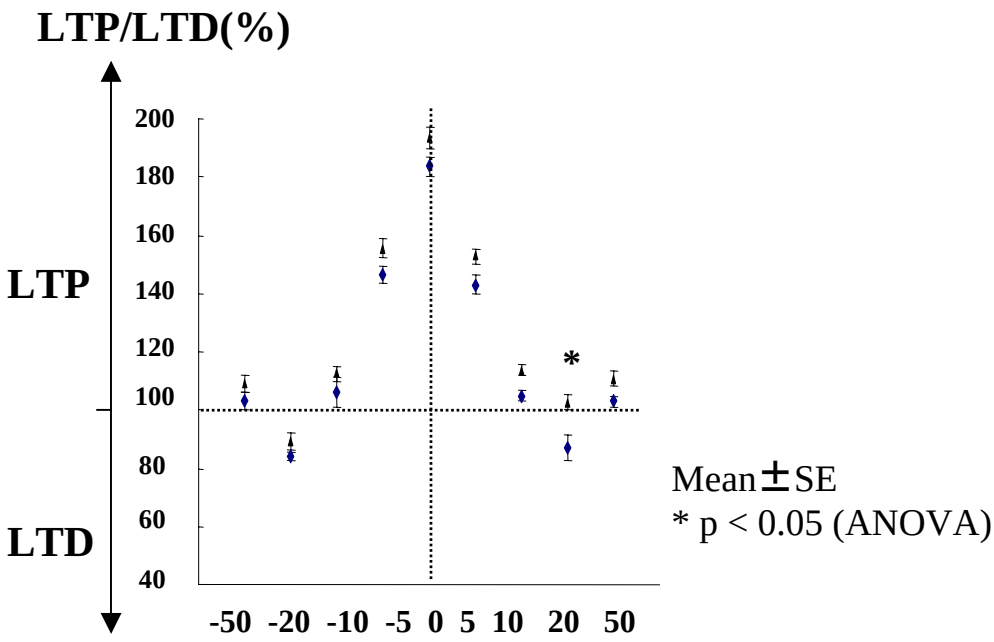
LTP/LTD(%)
LTP
LTD
200
180
160
140
120
100
80
60
40
*
-50 -20 -10 -5 0 5 10 20 50
Relative timing (ms)
Mean±SE
* p < 0.05 (ANOVA)

Fig. 6

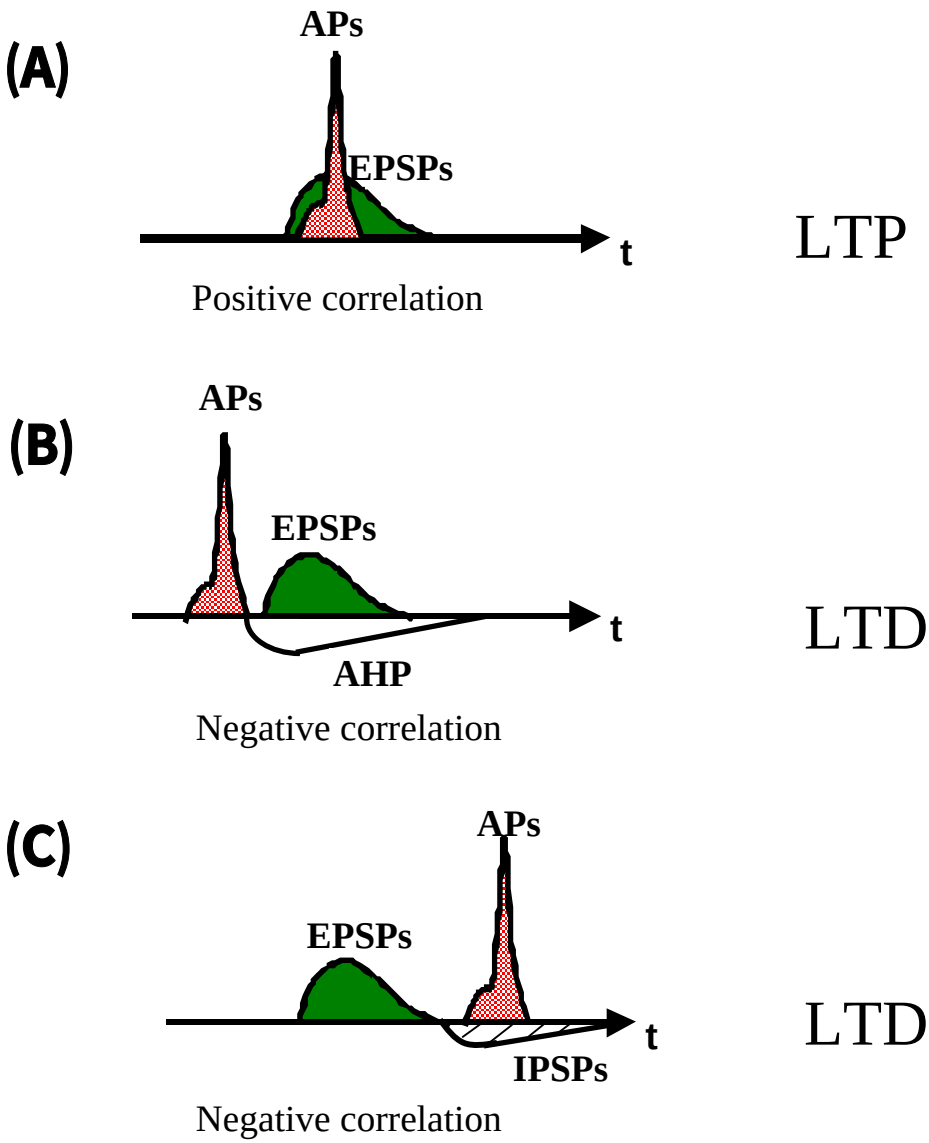
(A)
APs
EPSPs
t
LTP
Positive correlation
(B)
APs
EPSPs
t
AHP
LTD
Negative correlation
(C)
APs
EPSPs
t
IPSPs
LTD
Negative correlation

Fig. 7