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Fimbrial Control of Bidirectional Synaptic Plasticity of Medial Perforant Path-Dentate Transmission

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ABSTRACT Lesions of the fimbria-fornix (FF) tract cause profound impairments of cognitive ability in animals. Our previous study showed that spatial performance correlates with long-term potentiation (LTP) of the dentate gyrus (DG), but not of the CA1 region, in rats with bilateral FF lesions, suggesting that FF lesions selectively inhibited LTP in the DG. The cortical input to the DG is anatomically and physiologically divided into two types of afferents, i.e., the medial perforant path (MPP) and the lateral perforant path (LPP), which show distinct synaptic properties. To elucidate the difference in the FF modulation of these two inputs, field responses were recorded from MPP- or LPP-DG synapses in anesthetized rats. MPP-DG synapses of rats with FF lesions displayed neither LTP in response to theta-burst stimulation nor long-term depression (LTD) in response to low-frequency burst stimulation. In contrast to the MPP, LPP-DG synapses showed normal LTP in rats with FF lesions. The low-frequency burst stimulation could not induce LTD at LPP-DG synapses in either intact or FF-lesioned rats. These results suggest that the FF pathway selectively supports the mechanisms of bidirectional synaptic plasticity at MPP-DG synapses. This study provides new insights into external control of information processing in the hippocampus. **Synapse 47: 163–168, 2003.**

INTRODUCTION

The neural substrates of information processing and storage are most likely to involve activity-dependent long-lasting changes in synaptic strength. Two forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength, are induced by patterned activity of the afferent pathway and widely considered as a potential cellular basis of learning and memory (Bliss and Collingridge, 1993; Martin et al., 2000; Braunewell and Manahan-Vaughan, 2001). The mechanisms of hippocampal LTP and LTD have been revealed by a series of pharmacologic, biochemical, and genetic experiments (Nicoll and Malenka, 1995). Most of these studies have been performed by using isolated hippocampal slices in vitro. However, slice preparations have no afferent or efferent of the hippocampal formation, in which the property of LTP and LTD may not accurately reflect the natural function of the hippocampus in vivo.

The fimbria-fornix (FF), one of the principal fiber tracts in the central nervous system, reciprocally connects the hippocampus with the subcortical and cortical areas (Cassel et al., 1997). Lesions of the bilateral FF are known to produce profound impairments of spatial performance in a variety of maze tasks (Cassel et al., 1998; Hannesson and Skelton, 1998). The impairment may partly result from the deprivation of subcortical cholinergic innervations from the medial septum to the hippocampus. Indeed, the activities of choline acetyltransferase and acetylcholinesterase (AChE), both of which are cholinergic marker enzymes, are substantially reduced in the hippocampus after FF lesions. The spatial cognitive deficits can be partially reversed by transplantation of cholinergic neuron-rich fetal tissues into the hippocampus, while cholinergic

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neuron-poor tissues are ineffective (McNamara and Skelton, 1993; Dunnett, 1991; Haroutunian et al., 1985).

We and others indicated that FF lesions prevented the induction of LTP at perforant path – dentate gyrus (DG) synapses (Bergado et al., 1996; Abe et al., 1992; Valjakka et al., 1991; Nakao et al., 2001). This probably contributes, at least in part, to FF lesions-induced cognitive deficits (Nakao et al., 2001). Interestingly, however, rats with FF lesions display normal LTP in the CA1 region (Kleschevnikov et al., 1994; Nakao et al., 2001), even though FF lesions cause a decrease in AChE activity of CA1 as well (Nakao et al., 2001). We therefore assumed that the FF pathway does not equally influence neurotransmission at diverse types of hippocampal synapses. The perforant path consists of the medial perforant path (MPP) and the lateral perforant path (LPP). To date, no comparison has been conducted for LTP at MPP-DG and LPP-DG synapses in rats with FF lesions. In the present study, we investigated LTP at both synapses by applying theta-burst stimulation at various frequencies. In addition, we report the effect of FF lesions on the induction of LTD.

MATERIALS AND METHODS

Surgery

Experiments were performed according to the Japanese Pharmacological Society guide for the care and use of laboratory animals. Male Wistar/ST rats (SLC, Shizuoka, Japan), 240–300 g, were deeply anesthetized with pentobarbital (50 mg/kg, i.p.) and then fixed in a stereotaxic headholder, with the bregma and lambda kept horizontal. The FF was bilaterally transected by inserting a razor blade (6.0 mm in width) to a depth of 5.0 mm at 1.1 mm posterior to bregma. Sham operation was performed with the same surgical procedure except for the blade insertion of 1.0 mm in depth. Intact rats did not receive surgery. Electrophysiological experiments were conducted 14 ± 5 days after the surgery unless otherwise specified.

Histology

After electrophysiological recordings, the accuracy of FF lesions was validated with histochemical detection of AChE activity. The brains were removed and immediately frozen at −40°C. Each brain was sagittally cut into 20-μm-thick sections. The section was fixed with 4% paraformaldehyde and 0.2% picric acid for 24 h. AChE activity was detected by a modified thiocholine method of Patre et al. (1993). Because of a substantial decrease in AChE activity in the DG, we confirmed that FF lesions were successfully conducted in our experimental conditions (Fig. 1C). The AChE activity in the hippocampus of rats immediately after the FF-lesion operation (Fig. 1B) was comparable to that of intact rats (Fig. 1A).

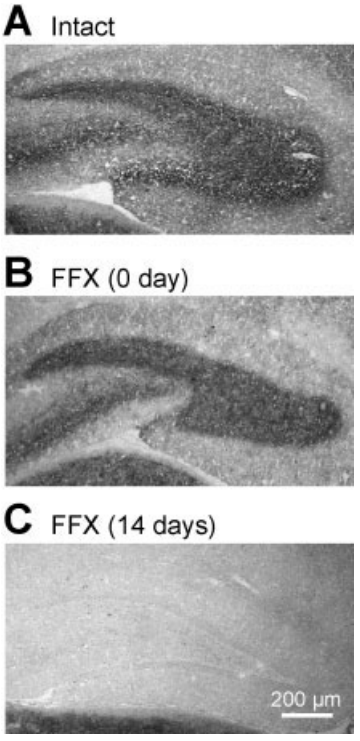

Fig. 1. Representative histochemical AChE staining of hippocampal sections of an intact rat (**A**) or a rat 1 h (**B**) or 14 days after FF lesions (**C**). FFX: FF lesion.

Field potential recording

Rats were anesthetized with a combination of urethane (1 g/kg, i.p.) and α-chloralose (25 mg/kg, i.p.) and fixed in a stereotaxic frame. To record field excitatory postsynaptic potentials (fEPSP), a tungsten recording electrode was inserted into the dentate molecular layer (3.5 mm posterior, 2.0 mm lateral to bregma) and bipolar stainless steel stimulating electrodes were placed along the MPP (8.1 mm posterior, 4.0 mm lateral to bregma) or the LPP (8.1 mm posterior, 5.0 mm lateral to bregma) (Christie and Abraham, 1994). Single-pulse test stimulation (80-μs duration) was applied at intervals of 30 sec, and its intensity was adjusted to produce a fEPSP with a slope of approximate 50% of maximum. Input-output (I–O) curves were constructed by sampling field potentials evoked by stimulation with increasing intensity ranging from 0–800 μA.

In order to induce LTP, theta-burst stimulation (TBS) consisting of five bursts (each one pulse, each two pulses at 50 Hz, each five pulses at 100 Hz, or each 20 pulses at 400 Hz) at 5 Hz was applied four times every 30 sec to the MPP and LPP (Fig. 2). LTD was induced by low-frequency burst stimulation (LFBS) consisting of 600 bursts (each four pulses at 250 Hz) at 1 Hz. The LFBS can reproducibly induce LTD in vivo and it is more efficacious in this regard than simple low-frequency stimulation, such as 900 pulses at 1 Hz (Takita et al., 1999; Izaki et al., 2000).

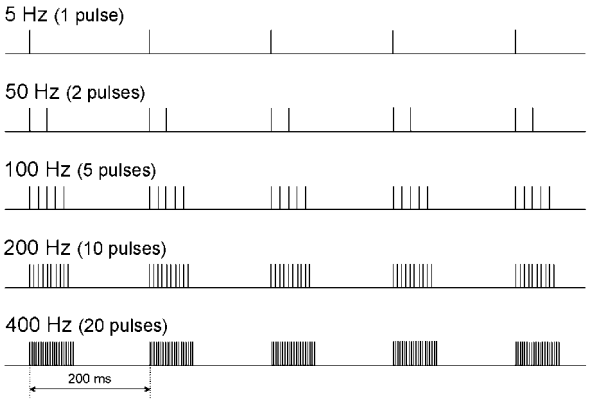

Fig. 2. TBS conditions used to induce LTP. Each TBS consists of five bursts at 5 Hz. Each burst consists of one pulse, two pulses at 50 Hz, five pulses at 100 Hz, 10 pulses at 200 Hz, or 20 pulses at 400 Hz. Four TBSs were applied at intervals of 30 sec to the MPP or LPP.

RESULTS

Upward shift in the I–O curve of fEPSP slopes in rats with FF lesions

Characteristic field potentials were evoked in the dentate molecular layer following single-pulse stimulation of the MPP (Fig. 3A). At a lower current of stimulus intensity (40 and 80 μA), fEPSP was observed as a simple negative trace, while a population spike was superimposed upon the fEPSP at higher current levels (150 and 270 μA). The I–O relationship at MPP-DG synapses is plotted in Figure 3B. Fourteen days after FF lesions, the I–O curve was significantly shifted upward ($F(2, 506) = 10.55$, $Q(2, 506) = 6.50$, $P < 0.01$, Tukey's test after two-way ANOVA) (Fig. 3B), suggesting an enhancement of synaptic excitability. No shift in the curve was detected in sham-operated rats ($P > 0.1$, data not shown) or rats immediately (1 h) after FF lesions ($Q(2, 506) = 2.08$, $P > 0.1$) (Fig. 3B). As synaptic responses were evoked by stimulation of the LPP, the I–O curve was shifted upward 14 days after FF lesions ($F(1, 297) = 67.22$, $Q(2, 297) = 11.59$, $P < 0.01$) (Fig. 3C).

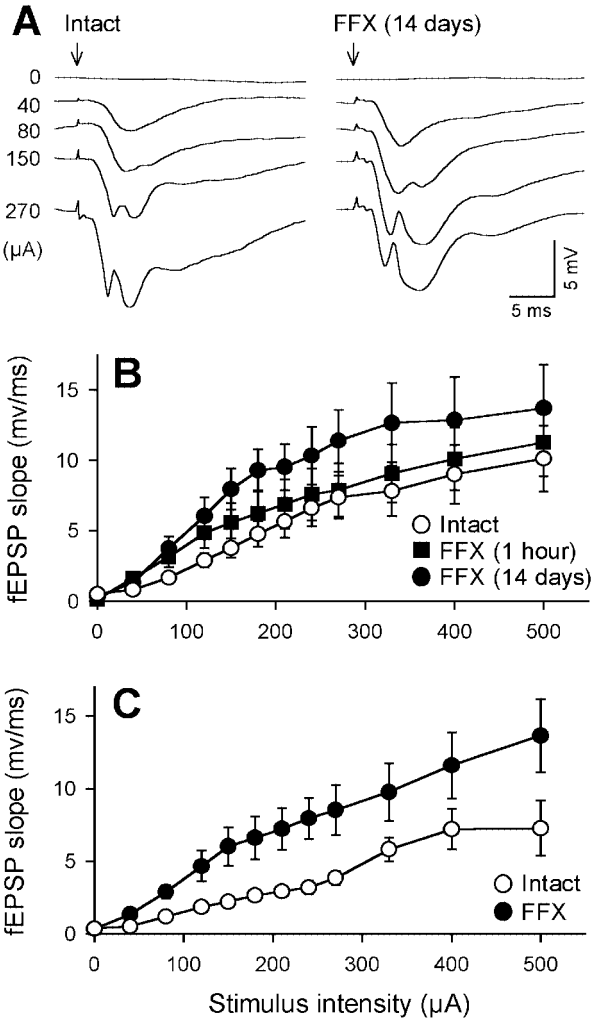

Fig. 3. Upward shift in the I–O curve of fEPSP slopes at MPP-DG synapses and LPP-DG synapses of rats with FF lesions. **A:** Sample records of the DG field potentials evoked by single-pulse stimulation of the MPP at various intensities (0–270 μA) in an intact rat (left) and a rat 14 days after FF lesions (right). Stimulation was delivered at the time indicated by the arrows. **B:** The I–O curves at MPP-DG synapses of intact rats (open circles) or rats 1 h (closed squares) or 14 days after FF lesions (closed circles). **C:** The I–O curves at LPP-DG synapses of intact rats (open circles) or rats 14 days after FF lesions (closed circles). FFX: FF lesion. Data are means ± SEM of 12–18 animals.

Selective impairment of LTP and LTD at MPP-DG synapses after FF lesions

To determine whether FF lesions affect the induction of LTP at MPP-DG synapses, a 200-Hz TBS was applied to the MPP. In intact rats, MPP fEPSPs were immediately enhanced in response to the TBS and LTP was induced (Fig. 4A). The average change in fEPSP slopes 45–60 min after the TBS was 21.1 ± 6.4% (Fig. 4B) ($t(56) = 5.15$, $P < 0.001$ vs. nontetanized control, Student's t-test). Fourteen days after FF lesions, however, the fEPSPs were almost unchanged after the same application of TBS and no LTP was formed (Fig. 4A). The average change in fEPSP slopes at 45–60 min was −6.8 ± 6.9%, which was significantly less than that of intact rats ($t(10) = 2.90$, $P = 0.016$) (Fig. 4B). Normal LTP was induced in either sham-operated rats or rats immediately (1 h) after FF lesions (Fig. 4B).

We examined the TBS-frequency dependency of the effects of FF lesions on MPP LTP. TBS at either 5 Hz or 50 Hz did not induce LTP in intact rats or rats with FF lesions (Fig. 5A,B). When a 100-Hz TBS was delivered to the MPP, the fEPSPs were slightly potentiated, but the change was not significantly different from baseline ($t(54) = 1.77$, $P = 0.082$) (Fig. 5C). Application of a 400-Hz TBS to the MPP induced robust LTP in intact rats (Fig. 5D). In rats with FF lesions, fEPSPs were enhanced in the immediate aftermath of TBS but retuned to baseline. Taken together, FF lesions prevented MPP LTP (Fig. 5E).

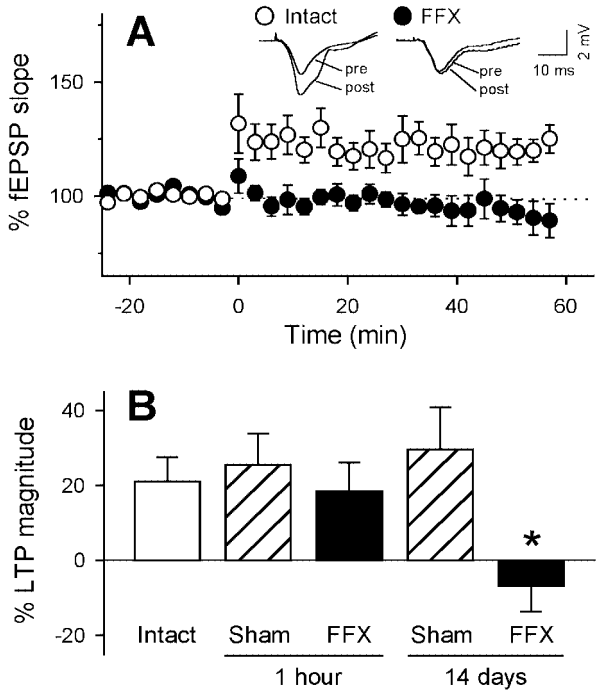

Fig. 4. Impairment of LTP at MPP-DG synapses in rats 14 days after FF lesions. **A:** Time course of changes in fEPSP slopes in anesthetized rats of intact (open circles, n = 7) and FF lesions (closed circles, n = 5). A 200-Hz TBS was applied to the MPP at time 0. Representative fEPSP recordings at time −4 (pre) and 60 (post) are shown in the inset. The ordinate is expressed as a percentage of baseline (time −25 to 0). **B:** The average of LTP magnitude 45–60 min after TBS in rats of intact (open column, n = 7), 1 h or 14 days after sham operation (hatched column, n = 4–6) and after FF lesions (closed column, n = 5). FFX: FF lesion. $*P < 0.05$ vs. Intact: Tukey's test after one-way ANOVA. Data are means ± SEM of n cases.

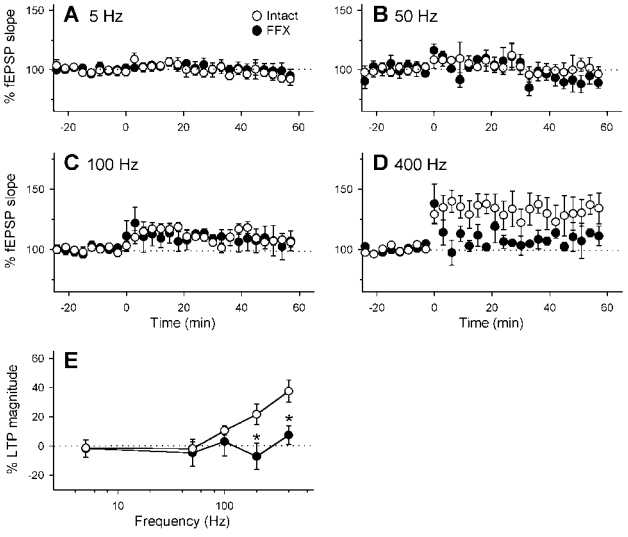

Fig. 5. Impairment of MPP LTP in response to TBS at various frequencies in rats 14 days after FF lesions. The MPP of intact rats (open circles) or rats with FF lesions (closed circles) was tetanized at 5 Hz (**A**), 50 Hz (**B**), 100 Hz (**C**), or 400 Hz (**D**) of TBS. **E:** Summary data for changes in synaptic strength 45–60 min after TBS. FFX: FF lesion. $*P < 0.05$ vs. Intact: Student's *t*-test. Data are means ± SEM of 4–7 cases.

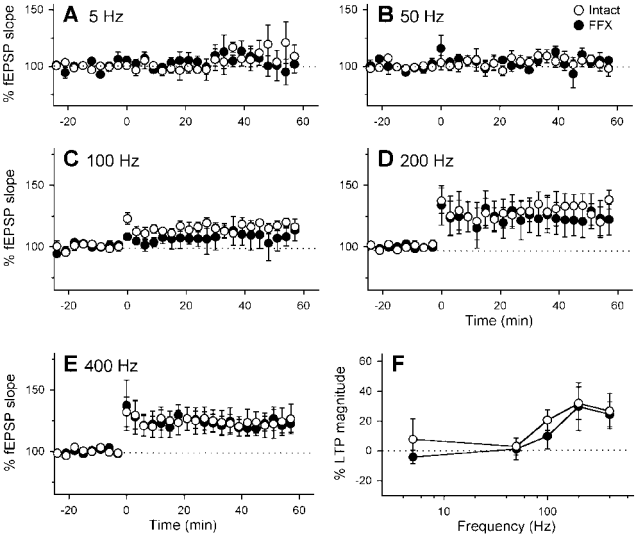

Fig. 6. Normal LTP at LPP-DG synapses of rats with FF lesions. The LPP of intact rats (open circles) or rats with FF lesions (closed circles) was tetanized at 5 Hz (**A**), 50 Hz (**B**), 100 Hz (**C**), 200 Hz (**D**), or 400 Hz (**E**) of TBS. **F:** Summary data for changes in synaptic strength 45–60 min after TBS. FFX: FF lesion. Data are means ± SEM of 4–5 cases.

To assess whether FF lesions also affect LTP at LPP-DG synapses, fEPSPs evoked by LPP stimulation were recorded from the dentate molecular layer. TBS at 5, 50, or 100 Hz induced no apparent LTP at these synapses, but both 200-Hz and 400-Hz TBSs produced robust LTP (Fig. 6A–E). The magnitude of LTP was not different between intact rats and rats with FF lesions (Fig. 6D,E). Thus, LPP LTP was not affected by FF lesions (Fig. 6F).

There is no report studying the modulation of the induction of LTD by the FF tract. Thus, we finally attempted to determine whether LTD was altered after FF lesions. In intact rats, homosynaptic LTD was reproducibly induced by application of LFBS to the MPP (Fig. 7). The average change in fEPSP slopes 45–60 min after LFBS was −20.3 ± 2.9% ($t(60) = 5.75$, $P = 0.008$ vs. nontetanized control, Student's *t*-test). In rats with FF lesions, fEPSPs were decreased after LFBS application but returned to baseline within 30 min. The average change in fEPSP slopes at 45–60 min was −3.1 ± 4.9%, which was significantly less than that of intact rats ($t(19) = 2.56$, $P = 0.018$). Therefore, FF lesions impaired the induction of LTD at MPP-DG synapses.

On the other hand, we failed to induce LTD at LPP-DG synapses; several patterns of LFBS were tried, but they caused LTP or no long-lasting changes. With respect to LTD induction protocols, therefore, LPP and MPP synapses were physiologically different. Thus, we could not examine the effect of FF lesion on LTD at LPP-DG synapses.

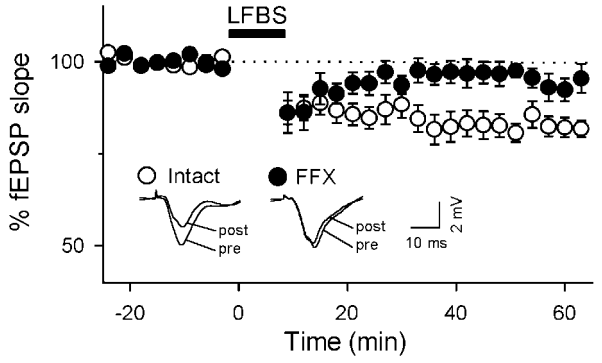

Fig. 7. Impairment of LTD at MPP-DG synapses in rats with FF lesions. LFBS was applied at time 0–10 in intact rats (open circles, n = 11) or rats with FF lesions (closed circles, n = 10). Representative fEPSP traces at time −4 (pre) and 60 (post) are shown in the inset. FFX: FF lesion. Data are means ± SEM of n cases.

DISCUSSION

The modulation of hippocampal function by other brain regions is still poorly understood. In the present study, we focused on the role of the FF, one of the principal fiber tracts in the brain, in hippocampal synaptic plasticity and have shown for the first time that FF lesions abrogated the induction of both LTP and LTD at MPP-DG synapses, sparing LTP at LPP-DG synapses.

What is the mechanism of the impairment of MPP LTP following FF lesions? We indicated that the I–O curve was shifted upward at MPP-DG synapses. Therefore, one possibility is that the LTP mechanism in rat with FF lesions was saturated before TBS application. If this is the case, FF lesions should occlude LPP LTP because the LPP I–O curve was also shifted upward after FF lesions. However, LPP LTP was normal. In addition, FF lesions abolished MPP LTD as well as LTP. This cannot be accounted for by the preexisting saturation of synaptic strength. Therefore, the change in basal responses is unlikely causal.

Cognitive deficits following FF lesions are believed to result from a lack of cholinergic innervation from the medial septum (Cassel et al., 1997). Thus, another possibility is that the LTP impairment after FF lesions is due to a decrease in cholinergic terminals at MPP-DG synapses. Indeed, a massive loss of AChE activity was found in the DG 14 days after FF lesions, while the AChE activity and LTP were both intact immediately after FF lesions. However, we do not believe that this loss of cholinergic afferents can fully explain the impairment of MPP LTP, because the decrease in AChE activity was not limited to MPP-DG synapses but also observed in the outer molecular layer, a recipient site of the LPP.

Although the MPP and LPP terminate in close proximity to each other in the dentate molecular layer, they possess quite different biochemical and physiological properties. Immunoreactivity for cholecystokinin is evident only in the MPP, whereas that for enkephalin is present only in the LPP (Fredens et al., 1984). Consistent with this, cholecystokinin and enkephalin facilitates the induction of MPP LTP and LPP LTP, respectively, but not vice versa (Bramham et al., 1988). Furthermore, MPP LTP is initiated by NMDA receptor-dependent mechanisms while the induction of LPP LTP is virtually independent of NMDA receptor activation (Dahl et al., 1990). Bath application of NMDA results instead in long-lasting depression at LPP synapses (Rush et al., 2001). The activity of opioid receptors is essential only for the induction of LPP LTP (Bramham, et al., 1991; Bramham and Sarvey, 1996). Therefore, the mechanism of MPP LTP is substantially different from that of LPP LTP. It is plausible that the FF tract selectively modulates the signaling pathways that mediate MPP LTP. Considering a report showing that the loss of the cholinergic innervation by the immunotoxin induced a significant enhancement in NMDA receptor-mediated transmission in the hippocampus (Jouvenceau et al., 1998), the cholinergic modulation of NMDA receptor activity is an unlikely cause of the selective effect of FF lesion on MPP LTP. The cholinergic system is also shown to reciprocally interact with cholecystokinin signaling. Cholecystokinin can activate or inhibit neural net activity. In the ventromedial hypothalamus, the action of cholecystokinin is suppressed by carbachol, a cholinergic agonist (Boden and Woodruff, 1994). On the other hand, cholecystokinin seems to prevent scopolamine-induced memory impairment (Itoh et al., 1988) and to increase the release of AChE in the striatum (Zelles et al., 1991). Contrary to these facilitatory effects of cholecystokinin, Lamour et al. (1983) observed that the excitatory action of AChE in the cerebral cortex could be reduced when cholecystokinin preceded its administration. Because cholecystokinin is selectively distributed at MPP synapses and contributes to the induction of MPP LTP (Fredens et al., 1984; Bramham et al., 1988), the dynamic interactions between cholecystokinin and AChE may account for the selective impairment of MPP LTP in rats with FF lesions.

The activity history has been suggested to influence its future responses to synaptic input in one prominent model of experience-dependent synaptic plasticity, often termed metaplasticity (Bienenstock et al., 1982). Experimentally, stimulation of the afferents over a range of frequencies produces a frequency–response curve of synaptic plasticity, i.e., LTP and LTD. Thus, a change in the LTD/LTP crossover point, i.e., a horizontal shift in the frequency–response curve, is believed to represent an experience-dependent mechanism that is capable of modifying the synaptic plasticity phenomena in developmental and learning/memory processes in the brain (Bienenstock, et al., 1982). However, FF lesions prevented the induction of MPP LTP without an apparent shift in the frequency–response curve. FF

lesions also prevented the induction of MPP LTD. These results imply that FF lesions completely deprive MPP-DG synapses of the capability of synaptic plasticity. Our previous study showed that FF lesions did not affect the induction of CA1 LTP (Nakao et al., 2001). It is likely, therefore, that among diverse neural circuits in the hippocampal formation, MPP synaptic plasticity is selectively vulnerable to FF lesions. Because FF lesions produce severe deteriorations of hippocampal-dependent memory, our findings underscore a pivotal role of the MPP in learning and memory. Therefore, it is intriguing to see that MPP synaptic efficacy is tightly under the control of external regions other than the hippocampus. This study will provide insights into the exterior modulatory system of hippocampal information processing.

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