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Attenuated hippocampal long-term potentiation in basolateral amygdala-lesioned rats

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Abstract

Possible involvement of the amygdaloid input in long-term potentiation (LTP) in the medial perforant path-dentate gyrus granule cell synapses in vivo was investigated by evaluating the effects of lesions of the amygdaloid nucleus. The dentate gyrus synaptic potential evoked by low-frequency test stimulation did not change following lesions of the basolateral and central amygdala. However, when tetanic stimulation (30 pulses at 60 Hz) was applied 60 min after lesioning of the ipsilateral basolateral amygdala, the magnitude of LTP was significantly attenuated. Since lesions of the ipsilateral central amygdala and the contralateral basolateral amygdala did not affect the dentate gyrus LTP, the attenuation of the dentate gyrus LTP is a specific effect of acute lesions of the ipsilateral basolateral amygdala. The basolateral amygdaloid lesions significantly attenuated both LTP induced by weak (20 pulses at 60 Hz) and strong (100 pulses at 100 Hz) tetanus, indicating that the effect of the lesions does not depend on the strength of tetanus applied to induce LTP. When the ipsilateral basolateral amygdala was destroyed after application of tetanus, it did not affect the established LTP. The attenuation of LTP was also observed after the basolateral amygdala-lesioned rats were allowed a recovery period of 2 weeks. This is the first report providing evidence that the ipsilateral basolateral amygdala modulates hippocampal synaptic plasticity in vivo.

Key words: Long-term potentiation; Hippocampus; Lesion; Basolateral amygdala; Amygdalo-hippocampal interaction

1. Introduction

Long-term potentiation (LTP) of evoked potentials in the hippocampus is a form of activity-dependent synaptic plasticity which may underlie learning and memory [3,4,29]. LTP has been studied mainly on synaptic mechanisms between intrinsic hippocampal neurons, while it has also been reported that the induction of hippocampal LTP is regulated by subcortical afferents to the hippocampus such as cholinergic input from the septal area [25], noradrenergic fibers from the locus coeruleus [13] and serotonergic afferents from the median raphe [19]. Modulation by extrinsic inputs is an important subject to elucidate the nature of LTP in vivo.

The amygdala is thought to be involved in certain types of learning and memory as well as emotional and motivational aspects of behavior [7,11,12,15,21]. Neural interactions between the amygdala and hippocampus were first suggested by Donglas and Pribram [8], and the existence of synaptic inputs from the amygdala to the dentate gyrus of the hippocampus has been demonstrated by several neurophysiological experiments. Thomas et al. [30] reported that single-pulse stimulation of the amygdala evoked synaptic potentials in the dentate gyrus and that the dentate gyrus response to perforant path stimulation was enhanced by the preceding stimulation of the amygdala. Finch et al. [10] presented evidence for monosynaptic and excitatory projections from the amygdala to the entorhinal cortex. Racine et al. [24] observed LTP of evoked potentials in the dentate gyrus following amygdala stimulation. These earlier findings clearly suggest a functional amygdalo–hippocampal interaction, but there has been no report about the role of the amygdaloid inputs in the generation of hippocampal LTP. Therefore, in the present study, we investigated possible involvement of the amygdaloid inputs in the generation of LTP in the medial perforant path-dentate gyrus granule cell

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synapses by evaluating the influences of lesions of the amygdaloid nucleus. As a result we found that LTP of population spikes in the dentate gyrus was partially attenuated by lesions of the basolateral amygdaloid nucleus. The amygdaloid complex is divided into a basolateral and a cortical part, but recent behavioral studies have shown that, among subnuclei of the amygdala, the basolateral amygdala is particularly involved in learning and memory [9,14,22,31]. The finding in the present study will give further information about neural mechanisms by which the basolateral amygdaloid neurons contribute to memory function.

2. Materials and methods

2.1. Electrophysiology

Recording of evoked potential was made as described in our previous paper [16]. Briefly, male Wistar rats aged 7–11 weeks 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. A bipolar electrode was placed in the left entorhinal cortex to stimulate the medial perforant path and evoked potential was extracellularly recorded with a monopolar electrode positioned at the granule cell layer of the ipsilateral dentate gyrus. A single test stimulus (0.08 ms duration) was applied at intervals of 30 s, and the stimulus intensity was set to a level which produced a population spike of about 50% of the maximum. Tetanic stimulation to induce LTP was applied at the same stimulus intensity through the same electrode as used for test stimulation.

As shown in Fig. 1A, the field potential recorded from the dentate granule cell layer in response to medial perforant path stimulation is composed of slow positivity and sharp negativity. The slow positivity reflects mainly excitatory postsynaptic potential (EPSP), which is generated in dendritic spines and spreads along with the dendrites. The sharp negativity is a result of the synchronous firing of the granule cells and generally termed the population spike. To quantify changes of evoked potentials, we measured the following parameters: (i) the onset slope of field EPSP, (ii) the amplitude of population spike, (iii) the latency of population spike peak. The way of measuring these parameters is described in Fig. 1A in detail. Under the present experimental conditions, the percentage of the increase of field EPSP slope value following tetanic stimulation was always smaller than that of population spike. The effects of amygdaloid lesions on tetanus-induced LTP were therefore evaluated by employing the amplitude of population spike as a measure of overall changes in cellular responses.

2.2. Surgery

In order to observe acute effects of amygdaloid lesions, each rat received unilateral lesions of the amygdaloid nucleus while the evoked potentials were recorded under anesthesia as described above. The electrode (0.25 mm in diameter, 1 mm exposed tip) was stereotaxically inserted into the left (ipsilateral to the recording site) or right (contralateral) basolateral amygdala (2.8 mm posterior to bregma, 5.2 mm lateral to midline, 7.6 mm ventral to dura) or the ipsilateral central amygdala (2.8 mm posterior to bregma, 4.2 mm lateral to midline, 6.9 mm ventral to dura), and tissue lesions were caused by keeping the temperature of the electrode tip at 80°C for 10 s with a lesion generator (Muromachi Kikai, Tokyo, Japan). The rats which received only insertion of the electrode into the amygdaloid nucleus served as sham-operated group.

In order to observe chronic effects of lesions, rats were anesthetized with ketamine (50 mg/kg, i.m.) and given the amygdaloid lesions by the same procedure as described above. The sham-operated group received only insertion of the electrode into the amygdala. Two weeks after the surgery, recording of evoked potentials was made under anesthesia with urethane and α-chloralose as described above. The age-matched intact rats served as control.

2.3. Histology

After the completion of the experiment, the rats given acute amygdaloid lesions were sacrificed, and the brains were removed and cut into slices to verify the positions of electrode tips used for lesioning. The lesioned area, which looked transparent, could be distinguished from the surrounding intact area. The rats given chronic lesions were perfused with ice-cold phosphate buffered-saline (pH 7.4) containing 8% paraformaldehyde. The brains were removed and soaked in the same fixative for 24 h. After frozen, each brain was coronally sliced at 20 μm thickness with a microtome and stained with Lillie-Mayer's hematoxylin and eosin Y.

3. Results

First, we investigated the acute influences of amygdaloid lesions on the dentate gyrus synaptic potentials evoked by low-frequency test stimulation of the medial perforant path. As shown in Fig. 1, the ipsilateral basolateral amygdala was destroyed during recording of the dentate gyrus responses, but there was no apparent change in field EPSP and population spike. Lesions of the contralateral basolateral amygdala and the ipsilateral central amygdala also showed no influence on evoked potentials in the dentate gyrus ($n = 2$; data no shown).

Next we attempted to investigate the influences of amygdaloid lesions on the generation of LTP in the dentate gyrus. We have previously observed that lesions of the fimbria-fornix, a major pathway of subcortical afferents to the hippocampus, resulted in decreased probability of LTP generation in the dentate gyrus and the difference between the fimbria-fornix-lesioned and sham-operated group was most remarkably seen when a moderate tetanic stimulation (30 pulses at 60 Hz) was applied [1]. Therefore, the effects of amygdaloid lesions on LTP induced by the moderate tetanus were first compared. When a 30-pulse, 60-Hz tetanus was applied in intact rats, the amplitude of population spike was greatly potentiated and LTP was generated in all the five cases tested. The magnitude of LTP of population spikes in sham-operated group was not different from that in the intact group (Fig. 2). The magnitude of LTP induced by a 30-pulse, 60-Hz tetanus in the ipsilateral basolateral amygdala-lesioned rats was significantly smaller than that in the sham-operated rats (Fig. 2A). On the other hand, lesions of the ipsilateral central amygdala (Fig. 2B) or the contralateral basolateral amygdala (Fig. 2C) did not influence the induction of LTP. The placements of the electrode

tips used for lesioning were checked in all cases after the experiment (Fig. 3).

It was also examined whether or not the attenuation of LTP by the ipsilateral basolateral amygdala lesions depends on the condition of tetanic stimulation applied

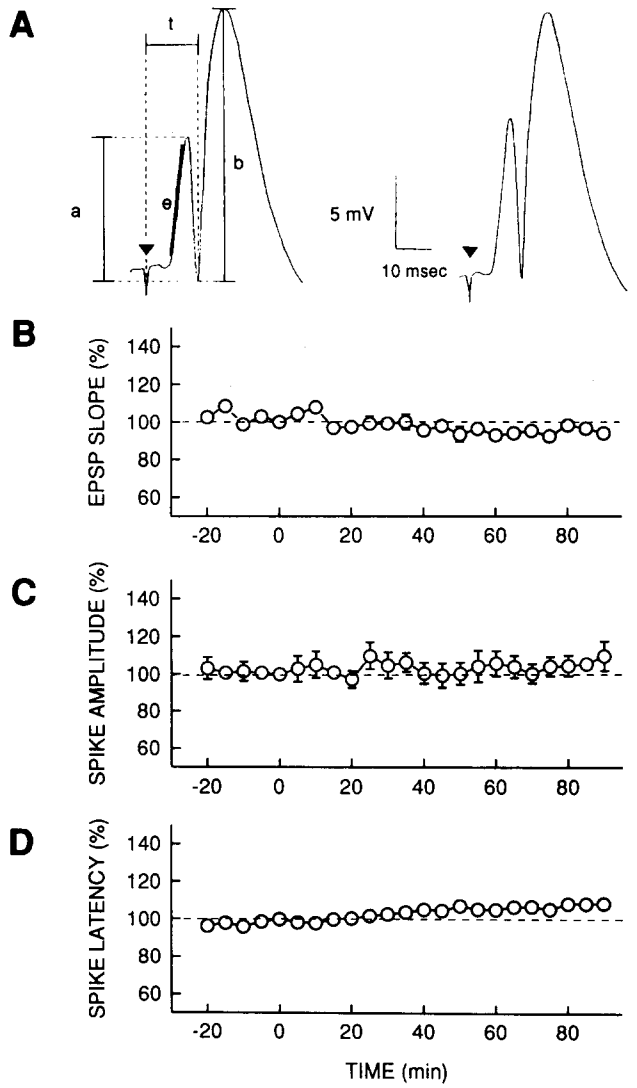

Fig. 1. Acute effects of lesions of the ipsilateral basolateral amygdala on basal synaptic potentials evoked by test stimulation in the medial perforant path-dentate granule cell synapses of anesthetized rats. A: typical records of evoked potentials in the dentate gyrus 2.5 min before (left) and 2.5 min after (right) lesioning of the ipsilateral basolateral amygdala. Test stimulation was delivered at the time indicated by arrowheads. The amplitude of the population spike was defined as the average of the amplitude from the first positive peak to the succeeding negative peak (a) and the amplitude from the negative peak to the second positive peak (b), i.e. (a+b)/2. The slope of field EPSP (e) and the latency of the population spike (t) were measured as indicated. B–D: changes in the EPSP slope (B), the population spike amplitude (C) and the population spike latency (D) following the ipsilateral basolateral amygdala lesion. The ipsilateral basolateral amygdala was lesioned at time 0 min and each parameter was expressed as a percentage of the baseline value immediately before the lesioning. The data are represented as the means ± S.E.M. of 4 cases.

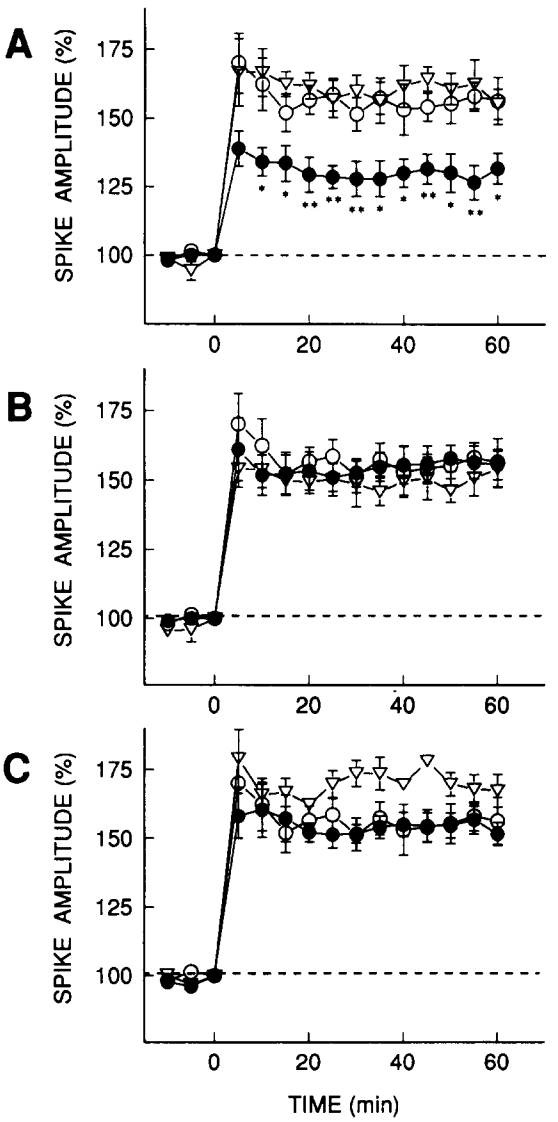

Fig. 2. Acute effects of lesions of the ipsilateral basolateral amygdala (A), the ipsilateral central amygdala (B) and the contralateral basolateral amygdala (C) on the induction of LTP. Tetanic stimulation (30 pulses at 60 Hz) was applied at time 0 min and population spike amplitude is expressed as a percentage of baseline value immediately before tetanus. The data for LTP in intact rats (○, $n = 5$) are shown in A, B and C in order to facilitate comparison. The sham-operated rats (▽) in A ($n = 4$), B ($n = 4$) and C ($n = 4$) received only insertion of the electrode into the ipsilateral basolateral amygdala, the ipsilateral central amygdala and the contralateral amygdala, respectively. The lesioned group (●) in A ($n = 5$), B ($n = 5$) and C ($n = 5$) had the respective amygdaloid nucleus destroyed 60 min prior to application of tetanus. All data are represented as the means ± S.E.M. of n cases. Asterisks indicate significant difference from the sham-operated group: * $P < 0.05$; ** $P < 0.01$; Duncan's multiple range test following analysis of variance (ANOVA).

to produce LTP (Fig. 4). Two different tetanic stimulations other than a 30-pulse, 60-Hz tetanus were tested to generate potentiation of evoked potentials. In intact rats, application of a 20-pulse, 60-Hz tetanus produced only a small potentiation of evoked potentials and this condition of tetanus was regarded as a threshold stimu-

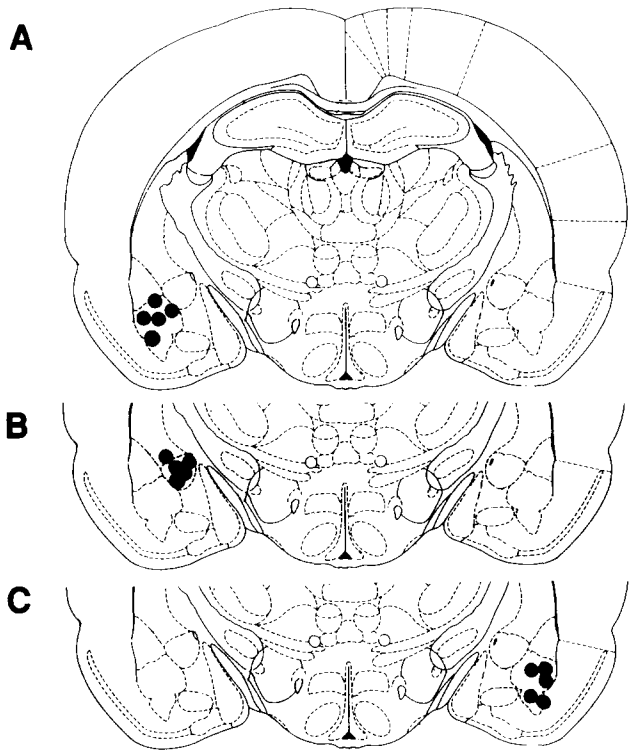

Fig. 3. Schematic drawings of amygdala electrode placements in the amygdaloid-lesioned group shown in Fig. 2. After the completion of the experiment, the rats given lesions of the ipsilateral basolateral amygdala (A), the ipsilateral central amygdala (B) and the contralateral basolateral amygdala (C) were sacrificed and the brains were coronally cut into slices to verify the positions of electrode tips used for lesioning. The diagrams show a coronal view of rat brain at a position 2.8 mm posterior to bregma. The lesioned sites are indicated by solid black circle.

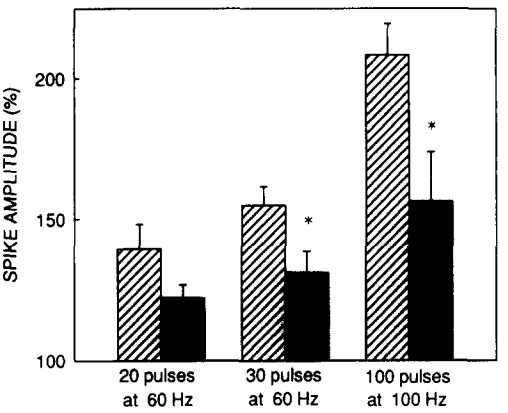

Fig. 4. Comparison of LTP induced by three different conditions of tetanus (20 pulses at 60 Hz, 30 pulses at 60 Hz, and 100 pulses at 100 Hz) in intact rats (hatched columns, $n = 5$) and rats given acute lesions of the ipsilateral basolateral amygdala (solid black columns, $n = 5$). The experimental procedures for lesioning and observation of LTP are the same as in Fig. 2. The amplitude of population spike following application of tetanus was expressed as a percentage of the basal value immediately before tetanus, and the average of percent amplitude of population spikes 30 to 60 min after tetanus was calculated to compare the magnitude of LTP produced in each group. All data are shown in the means ± S.E.M. Asterisks indicate significant difference from the intact group: * $P < 0.05$; Duncan's multiple range test following ANOVA.

lus required for generating LTP, while the magnitude of LTP induced by a 100-pulse, 100-Hz tetanus was larger than that by a 30-pulse, 60-Hz tetanus. When the basolateral amygdala was ipsilaterally lesioned 60 min prior to application of tetanus, the 20-pulse, 60-Hz tetanus-induced potentiation of population spikes was reduced but not completely disappeared. The LTP induced by a 100-pulse, 100-Hz tetanus was also partially attenuated by the lesions. Regardless of the strength of tetanus, the magnitude of LTP of population spikes in the basolateral amygdala-lesioned rats was about 50% of that in the intact rats.

The effect of acute amygdaloid lesions on the maintenance phase of LTP was also investigated. LTP was induced by application of a 30-pulse, 60-Hz tetanus and the ipsilateral basolateral amygdala was lesioned 20 min after the tetanus. As shown in Fig. 5, the basolateral amygdaloid lesions showed no influence on the established LTP.

In order to observe chronic effects of the lesions, the recording of evoked potentials was made two weeks after the lesioning of the ipsilateral basolateral amygdala. Body weights of rats after the surgery were normal and were not significantly different from those of intact rats (Fig. 6A). The wave form and amplitude of evoked potentials in the dentate gyrus of the basolateral amygdala-lesioned rats were not significantly different from those of the intact and sham-operated rats. The basal population spike amplitude before application of tetanus in the intact, sham-operated and amygdala-lesioned groups were 10.0 ± 1.2 mV ($n = 5$), 9.5 ± 1.7 mV ($n = 3$) and 9.5 ± 0.7 mV ($n = 5$), respectively. In the sham-operated group, application of a 30-pulse, 60-Hz tetanus produced LTP whose magnitude was the same as that in the intact group (Fig. 6B). On the other

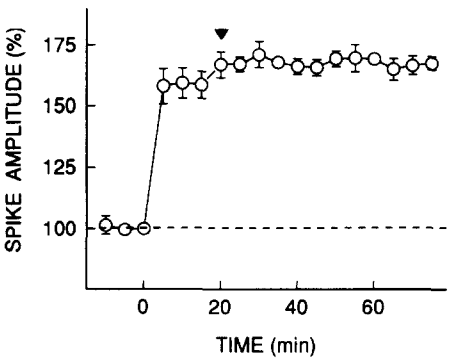

Fig. 5. The influence of acute lesions of the ipsilateral basolateral amygdala on the established LTP. LTP was induced by application of tetanus (30 pulses at 60 Hz), and then the ipsilateral basolateral amygdala was lesioned at the time indicated by an arrowhead (20 min after application of tetanus). The abscissa and ordinate are as in Fig. 2. Data are represented as means ± S.E.M. of 4 cases.

hand, in the basolateral amygdala-lesioned rats, the dentate gyrus LTP could be induced by application of a 30-pulse, 60-Hz tetanus, but the magnitude of LTP was significantly smaller than that in the sham-operated group (Fig. 6B). The magnitude of LTP in the basolateral amygdala-lesioned rats was about half of that in the sham-operated rats, very similar to the case of acute amygdaloid lesions. After the recording of evoked potentials, the extent of lesions of the amygdala was checked by histochemical observations (Fig. 7).

4. Discussion

The main finding in the present study is that the magnitude of LTP in the dentate gyrus is attenuated by lesions of the ipsilateral basolateral amygdala. The following evidence supports the idea that the attenuation of the dentate gyrus LTP following acute lesions of the basolateral amygdala is not due to a non-specific damage caused by surgical procedures: (i) the basal synaptic responses of the dentate granule cells were not affected by the lesioning; (ii) the lesions of the central amygdaloid nucleus, which neighbors on the basolateral amygdaloid nucleus, did not influence the generation of LTP at all; (iii) the attenuation of LTP was also observed after the operated rats were allowed a recovery period of two weeks. Furthermore, lesions of the contralateral basolateral amygdala did not affect the induction of LTP. Therefore, the present results suggest the involvement of the ipsilateral basolateral amygdala in the generation of LTP in the medial perforant path-dentate granule cell synapses.

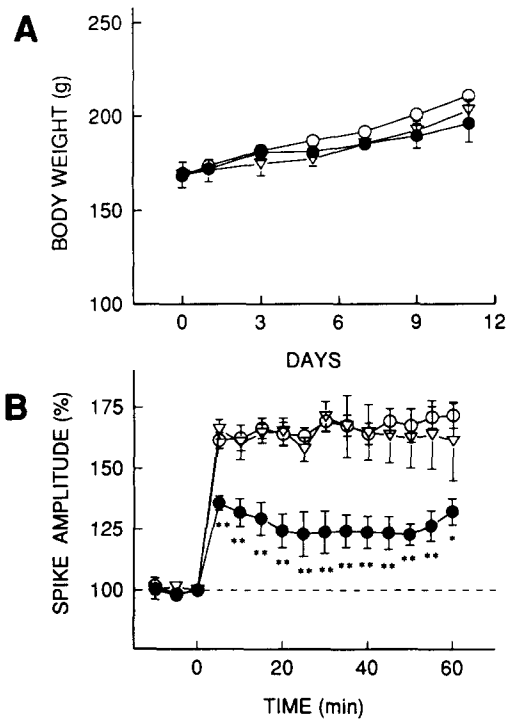

Fig. 6. Attenuation of LTP in the dentate gyrus of the rats given the basolateral amygdaloid lesions two weeks before. A: changes in body weights of rats after the surgery for lesioning. The sham-operated rats (▽, $n = 6$) and the basolateral amygdala-lesioned rats (●, $n = 6$) were weighed every 2 days after the surgery, comparing with the age-matched intact rats (○, $n = 7$). The abscissa indicates the days after the surgery. B: the dentate gyrus LTP induced by application of tetanus (30 pulses at 60 Hz) in the sham-operated rats (▽, $n = 3$), the basolateral amygdaloid-lesioned rats (●, $n = 5$) and the age-matched intact rats (○, $n = 5$). Two weeks after the lesioning surgery, the recording of evoked potentials was made under anesthesia. The abscissa and ordinate are as in Fig. 2. Asterisks indicate significant difference from the sham-operated group: * $P < 0.05$; ** $P < 0.01$; Duncan's multiple range test following ANOVA.

Generally, if the axons of presynaptic neurons are acutely transected, the propagation of spontaneous firing signal originating in the soma of presynaptic neurons is completely cut off, but application of electrical stimulation to the remaining presynaptic nerve endings normally evokes the postsynaptic potentials, indicating that the presynaptic nerve endings, even after the surgical isolation, retain the capability of releasing the neurotransmitter [17,28]. The present data that acute lesions of the basolateral amygdala, as well as chronic lesions, were sufficient to cause hippocampal hypofunction implies that the modulation of the dentate gyrus LTP by the amygdaloid inputs requires the propagation of electrical activity of the amygdaloid neurons rather than a basal release of neurotransmitters from the nerve endings. In this respect, it appears that the dentate gyrus LTP observed in hippocampal slice preparations in vitro does not involve the modulation by the amygdaloid inputs.

The cellular mechanism by which the basolateral amygdala contributes to the dentate gyrus LTP remains to be elucidated. Since the basolateral amygdaloid lesions did not affect the basal synaptic potentials evoked by low-frequency test stimulation, it is unlikely that neural inputs from the basolateral amygdala modulate excitability of dentate granule cells under normal condition. Furthermore, the basolateral amygdaloid lesions, when made after application of tetanus, did not affect the established LTP. Therefore, it is probable that the basolateral amygdaloid neurons regulate specifically the event during or following application of tetanus to the medial perforant path. The amygdaloid inputs may enhance the activity of presynaptic fibers, i.e. the perforant path, in response to high-frequency stimulation or the dentate gyrus granule cells may be in a state of heightened plasticity in the presence of amygdaloid inputs.

We have previously observed that, in the fimbria-fornix-lesioned rats, weak tetanus-induced LTP in the dentate gyrus completely disappeared but LTP was normally induced by application of strong tetanus [1]. It is probable that the subcortical afferents projecting

through the fimbria-fornix play a role in facilitating the generation of LTP, for example, adjusting the threshold of LTP induction, but are not necessary under condition of strong synaptic activation. On the other hand, the attenuation of LTP by lesions of the basolateral amygdala did not depend on the strength of tetanus applied to induce LTP, suggesting a different role for the basolateral amygdala from the fimbria-fornix. One possible explanation is that two different mechanisms, i.e. the basolateral amygdala-dependent and -independent mechanisms, are involved in the induction of LTP. Since, in the present study, LTP was observed as a population of changes occurring in many synapses, it is possible that the inputs from the basolateral amygdala are essentially required for the induction of LTP in some synapses but are not necessary in the other synapses. We are planning to measure LTP at individual synapses to reveal heterogeneity of the dentate gyrus synapses in terms of the modulation by the amygdaloid inputs.

Several projections from the amygdala to the entorhinal cortex or to the dentate gyrus have been demonstrated by several anatomical and physiological studies [2,10,26,27,30]. Which projection pathway is involved in the modulation of dentate gyrus LTP is not clear so far, but several points are suggested by the present data. First, the basolateral amygdaloid neurons unilaterally regulate the medial perforant path-dentate granule cell synapses, since the dentate gyrus LTP was attenuated by ipsilateral but not contralateral basolateral amygdala. Secondly, the amygdala has a projection to the hippocampus via the septal area and the fimbria-fornix [20], but this projection does not appear to be involved in the modulation of LTP, since the basolateral amygdala lesions attenuated the strong tetanus-induced LTP that was resistant to the fimbria-fornix lesions. Thirdly, the basolateral group of the amygdaloid nucleus mainly projects via the ventral amygdalofungal pathway, while the corticomedial group projects via the stria terminalis [6]. The result that lesions of central amygdaloid nucleus, which belongs to the corticomedial group, did not affect the generation of LTP in the dentate gyrus implies the importance of the amygdaloidfungal projection.

As described in the introduction, there has been several reports showing that, among subnuclei of the

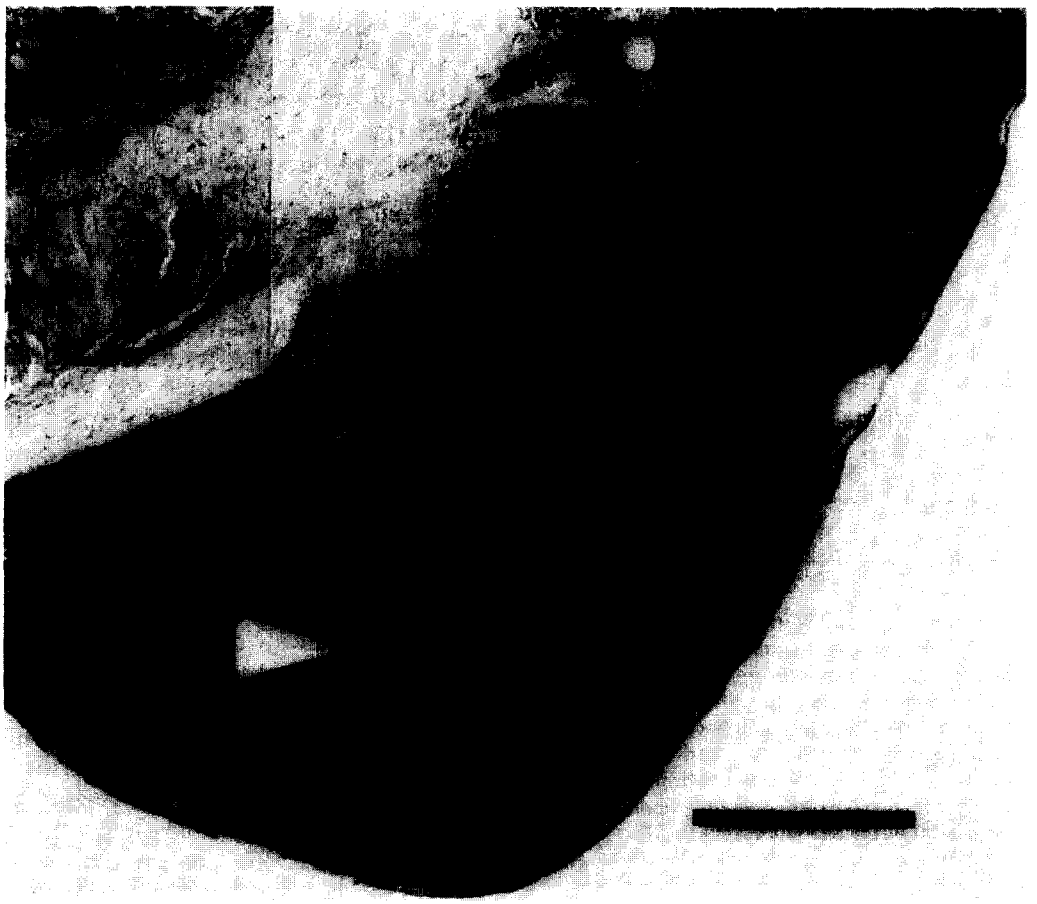

Fig. 7. A coronal section through the amygdala in a rat given the basolateral amygdaloid lesions 2 weeks before. After measurement of LTP shown in Fig. 6, the rats were perfused with paraformaldehyde and the coronal brain slices were stained with Lillie-Mayer's hematoxylin and eosin Y. A representative photograph is shown here. A white arrowhead indicates the lesioned part. Bar = 1 mm.

amygdaloid complex, the basolateral amygdala is particularly involved in certain types of learning and memory [9,14,31]. Ohno et al. [22] have reported that the impairment of working memory of basolateral amygdala-lesioned rats in the three-panel runway task recovered to control levels after postoperative re-training sessions, while hippocampal lesions have been reported to cause a severe and irreversible impairment of working memory in the same task. It is possible that the basolateral amygdala plays a modulatory but not essential role for establishing working memory. Considering our present data, the basolateral amygdala may contribute to the formation of memory, at least in part, by modulating hippocampal functions.

Kindling is an experimental epilepsy phenomenon in which the epileptogenic response to neural activation is permanently increased by the repeated application of high frequency electrical stimulation [23]. Recent studies have indicated that two models of synaptic plasticity, LTP and kindling-induced potentiation, may share aspects of an underlying neural mechanism [5]. Thus modulation of hippocampal plasticity by the amygdala may possibly serve as the cellular mechanism of kindling, and be also important in pathological aspects.

In conclusion, we have shown for the first time that lesions of the ipsilateral basolateral amygdala resulted in the attenuation of LTP in the medial perforant path-dentate granule cell synapses. This finding suggests a novel form of hippocampal LTP modulated by extrinsic inputs from the basolateral amygdala but also tells us that the role for the amygdala in learning and memory should be investigated taking into consideration the possibility that the amygdala affects memory functions by modulating hippocampal synaptic plasticity.

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