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Research report

Dentate gyrus field potentials evoked by stimulation of the basolateral amygdaloid nucleus in anesthetized rats

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Abstract

We previously found that long-term potentiation (LTP) in the dentate gyrus (DG) is attenuated by lesion of the basolateral amygdala (BLA), but it remained unclear whether or not there is neural connection between the BLA and the DG. In the present study, we tried to provide physiological evidence that the DG receives neural inputs from the BLA. Single-pulse electrical stimulation of the BLA evoked two distinct components of field potentials in the ipsilateral DG: the P1 component with 26-ms peak latency was elicited by lower intensity of BLA stimulation, whereas the P2 component with 14-ms peak latency was elicited at higher stimulus intensity. The P1 response (1) was evoked when the stimulating electrode was positioned within the BLA, (2) showed the laminar profile similar to the perforant path (PP)-evoked response and (3) exhibited strong paired-pulse facilitation. On the other hand, the P2 wave (1) was evoked even with the stimulating electrode outside the BLA, (2) did not reverse its polarity at any location in the DG and (3) showed only slight facilitation by paired-pulse stimulation. These data indicate that the P1 component represents synaptic responses of DG granule cells to neural inputs from the BLA. Furthermore, the BLA-evoked DG field potentials were not affected by local injection of tetracaine into the PP and displayed LTP independently of the PP-evoked response, suggesting that neural inputs from the BLA are not mediated by the PP.

Keywords: Basolateral amygdala; Dentate gyrus; Field potential; Paired-pulse facilitation; Long-term potentiation; Amygdalo-hippocampal interaction; Anesthetized rat

1. Introduction

The amygdala plays an important role in learning and memory associated with emotion [5,6,15,17,22]. Recent behavioral studies have provided evidence that the amygdala modulates hippocampal-dependent memory [16,18]. Furthermore, we have recently found that long-term potentiation (LTP) in the dentate gyrus (DG) of anesthetized rats is attenuated by surgical lesion of the basolateral amygdaloid nucleus (BLA) or by injection of a local anesthetic tetracaine into the BLA [8,9], suggesting that hippocampal synaptic plasticity is modulated by neural inputs from the BLA.

Neural projections from the amygdala to the hippocampus have been generally demonstrated by physiological studies [20,21]. Furthermore, McGaugh and colleagues [3,19] have recently reported that c-*fos* is highly expressed in the DG following injections of *N*-methyl-D-aspartate into the amygdala, providing evidence of a direct functional connection between the amygdala and the DG. However, there has been no report describing especially neural connections from the BLA to the DG. Therefore, in the present study, we tried to provide physiological evidence that the DG receives neural inputs from the BLA.

2. Materials and methods

The DG field potentials were recorded as described in our previous paper [11]. Male Wistar rats 7–9 weeks old were anesthetized with urethane (1 g/kg, i.p.) and α-chloralose (25 mg/kg, i.p.), and placed in a stereotaxic frame, with bregma and lambda in the horizontal plane. Bipolar stimulating electrodes were placed in the medial perforant path (PP) and the BLA, and the evoked responses were extracellularly recorded from the granule cell layer of DG. The stereotaxic coordinates of stimulating and recording sites are as follows: PP (8.1 mm posterior to bregma, 4.4 mm lateral to midline, 3.0 mm ventral to dura), BLA (2.8 mm posterior to bregma, 5.2 mm lateral to midline, 7.6 mm ventral to dura), DG (3.5 mm posterior to bregma, 2.0

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mm lateral to midline, 3.5 mm ventral to dura). Unless especially stated in the text, stimulating and recording electrodes were positioned at these basic coordinates. Single-pulse test stimulation consisted of monophasic square wave pulse (0.08 ms duration) and was delivered at intervals of 30 s or longer. Intensity of test stimulation set in each experiment is described in the text or figure legends. To induce LTP, tetanic stimulation (100 Hz for 1 s, twice at an interval of 30 s) was applied to the PP or BLA at the same stimulus intensity through the same electrode as used for test stimulation. The signals were passed through an analog-to-digital converter (Nihon Kohden EA-602J, Tokyo, Japan) for on-line averaging and recorded on an ink-writing oscillograph. The traces shown in the figures are averages of four consecutive records.

The placement of recording electrode in the DG was assessed by the characteristic waveforms evoked by PP stimulation. The excitatory postsynaptic potential (EPSP) evoked by PP stimulation was observed as a slow positive wave in the DG granule cell layer (see asterisks in Fig. 1A). If the stimulation is strong enough, a sharp negative-going 'population spike' appears superimposed upon the EPSP wave (see dots in Fig. 1A). The placement of the amygdaloid stimulating electrode was checked by histochemical observations as described in our previous paper [10]. Briefly, at the end of each experiment, stimulating sites were marked by small lesions, and coronal sections of each brain were stained with cresyl violet. Microscopic examination of the histological sections confirmed that we had stimulated precisely the intended amygdaloid nuclei in all rats.

To inactivate the PP, a stainless steel cylindrical cannula (0.5 mm o.d., 0.35 mm i.d.) connected to a micrometer syringe was stereotaxically placed 0.3 mm anterior to the PP stimulating electrode, and 100–200 nmol tetracaine (100–200 mM, 1 μl) was injected at a rate of 1 μl/min. At the end of each experiment, the placement of tip of microinjection cannula was checked by injecting a dye methyl blue through the cannula.

3. Results

3.1. Does BLA stimulation evoke field potentials within the DG?

Single-pulse stimulation of the ipsilateral BLA evoked characteristic field potentials in the DG granule cell layer (Fig. 1B). The ipsilateral BLA stimulation at low current levels (10–40 μA) produced a single positive-going potential with a peak latency of 25.7 ± 2.5 ms ($n = 8$). This low-threshold potential was designated as P1. The latency of P1 wave was little shifted with increasing stimulus intensity. The ipsilateral BLA stimulation at higher current levels (usually > 40 μA) produced another positive-going potential with a short peak latency (13.8 ± 1.3 msec, $n = 8$). As the stimulus current was increased, the high-threshold potential (P2) increased in size. In contrast to the ipsilateral BLA stimulation, the contralateral BLA stimulation evoked no apparent field potential in the DG ($n = 5$, Fig. 1C), suggesting that a neural connection from the BLA to the DG is unilateral and ipsilateral. In the follow-

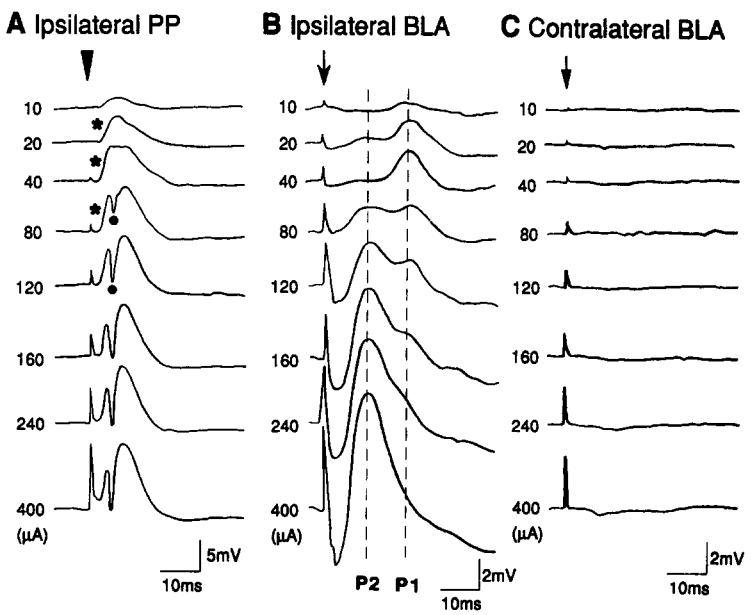

Fig. 1. Stimulus-response relationship of DG field potentials evoked by PP or BLA stimulation. The stimulating electrode was placed in the ipsilateral PP (A) or in the ipsilateral BLA (B) or in the contralateral BLA (C), and the evoked field potential was recorded from the DG granule cell layer. Single-pulse test stimulation was applied at current levels shown on the left of each trace. Representative records with one rat are shown here. Similar results were obtained with other five rats.

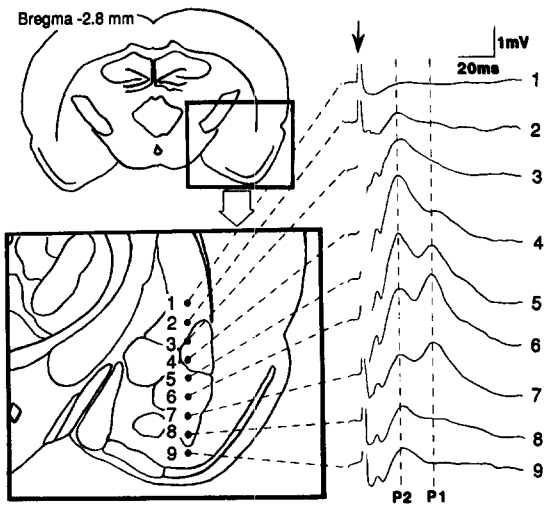

Fig. 2. Origin of BLA-evoked DG field potentials. The stimulating electrode was positioned at different depths throughout the BLA and single-pulse test stimulation (100 μA) was applied. The evoked field potentials were monitored with a recording electrode fixed in the DG granule cell layer. The position 6 corresponds to the basic coordinate of BLA stimulating electrode used in other figures. All traces shown here were obtained with one rat. Similar results were obtained with other three rats.

ing experiments, only the ipsilateral BLA and PP was stimulated.

To certify that these responses originate from the BLA only, the stimulating electrode was positioned at different depths through the BLA, and changes of DG field potentials were observed (Fig. 2). The P1 response was elicited when the stimulating electrode was positioned within or very close to the BLA (traces 4–8 in Fig. 2). The spot which elicited maximal P1 response was approximately the center of the BLA (trace 6 in Fig. 2). On the other hand, the P2 wave was elicited even when the stimulating electrode was positioned outside the BLA (traces 2–9 in Fig. 2).

To determine if the BLA-evoked potentials reflect the responses of the DG granule cells, the laminar profile was checked by moving the recording electrode. As well known, the PP makes a synaptic connection with the dendrites of the DG granule cells in the molecular layer. Stimulation of the PP produces a characteristic field EPSP, which is observed as a negative wave in the molecular layer and as a positive wave in the granule cell layer (see asterisks in Fig. 3A). The BLA-evoked P1 wave, which was positive-going in the granule cell layer, was observed as a negative-going wave in the molecular layer (see trace 2 in Fig. 3B and C) and disappeared when the recording electrode was above the molecular layer (trace 1 in Fig. 3B and C). The P1 wave reversed polarity at the inner one-third of the molecular layer, and the negative-going P1 amplitude was greatest in the center of the molecular layer (Fig. 3D). The laminar profile of P1 wave was similar to that of the PP-evoked EPSP component, indicating that the P1 wave reflects the dendritic responses of DG granule cells. On the other hand, the P2 wave did not reverse polarity at any location in the DG (Fig. 3B).

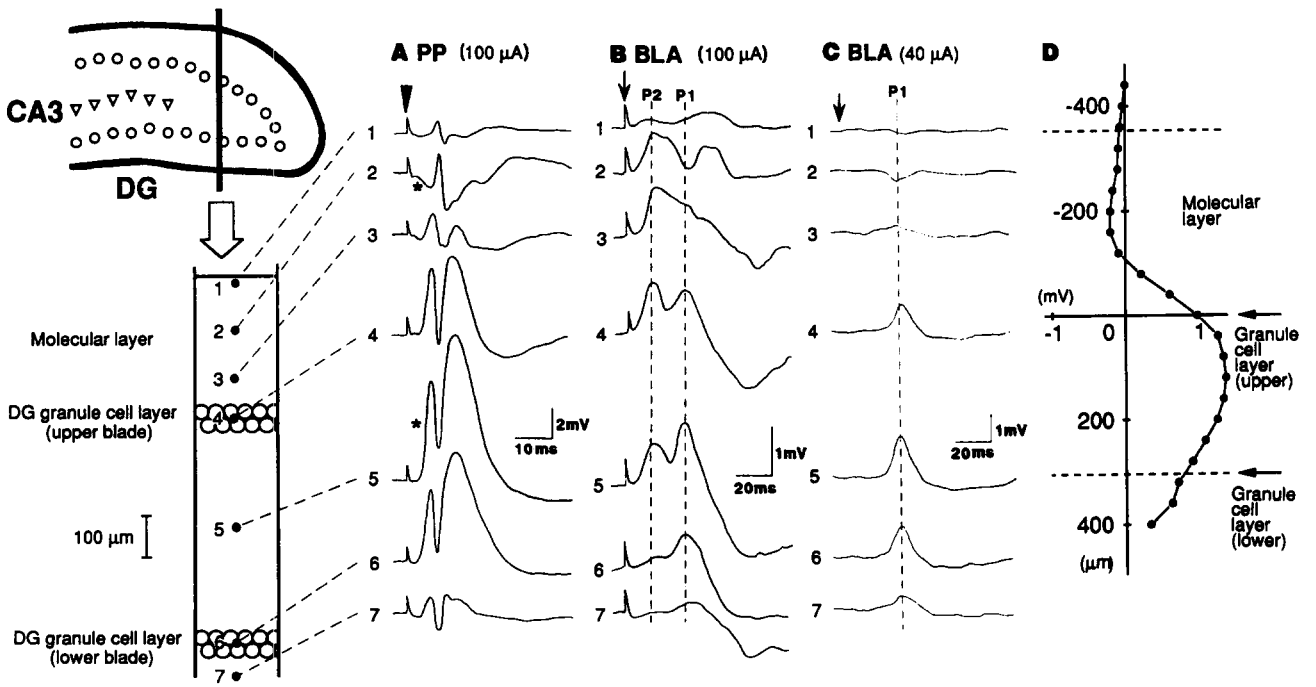

Fig. 3. Laminar profile of DG field potentials evoked by stimulation of the PP or BLA. Single-pulse test stimulation was applied to the PP (A, 100 μA) or BLA (B, 100 μA; C, 40 μA), and the evoked field potentials were monitored from different portions within the DG. More frequent samples were taken on the same condition as in C and the data are graphed in D, where voltage levels at the P1 peak latency are plotted against the recording depths. All traces shown here were recorded with one rat. Similar results were obtained with other four rats.

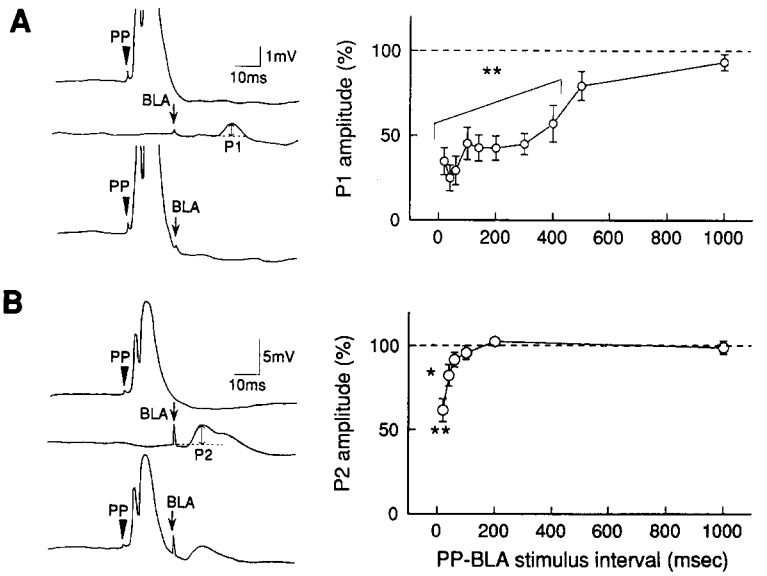

Fig. 4. Prestimulation of the PP occludes DG field potentials evoked by BLA stimulation. The intensity of PP test stimulation was always set for 100 μA. In A, the intensity of BLA stimulation was set for 40 μA and changes in P1 wave were examined. In B, the intensity of BLA stimulation was set for 120 μA and changes in P2 wave were examined. Left panels show sample records in which the PP was stimulated 20 ms prior to the BLA. In right panels, P1 or P2 wave amplitude was expressed as a percentage of the control response (no PP prestimulation) and plotted as a function of the PP-BLA stimulus interval. The data are represented as the means and S.E.M. (A, $n = 6$; B, $n = 6$). * $P < 0.05$, ** $P < 0.01$, Duncan's multiple range test.

If neural inputs from the BLA, like the PP, terminates in the DG granule cells, prestimulation of the PP might occlude BLA-evoked responses. As shown in Fig. 4, PP prestimulation significantly suppressed the field potentials evoked by BLA stimulation. The PP prestimulation caused strong suppression of the BLA-evoked P1 wave, which was observed for interpulse intervals up to 500 ms (Fig. 4A), whereas suppression of P2 wave was observed only for short (< 50 ms) interpulse intervals.

3.2. Do the BLA-evoked potentials represent synaptic responses?

When the same afferent pathway is electrically stimulated twice in rapid succession, the second stimulation

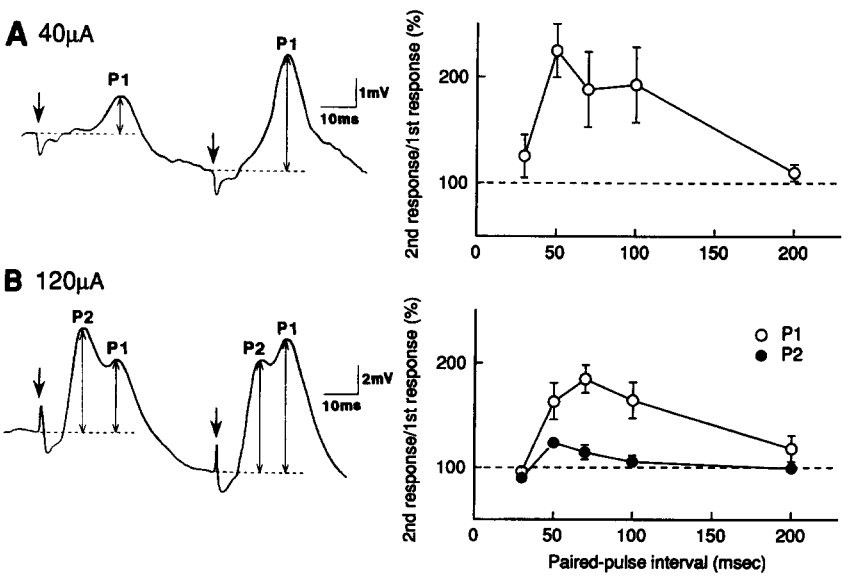

Fig. 5. Paired-pulse facilitation of BLA-evoked DG field potentials. Intensity of BLA test stimulation was set for a low current level (40 μA) in A and for a high current level (120 μA) in B. Left panels: sample records in which the BLA was stimulated (arrows) twice at an interval of 50 ms. Amplitude of responses evoked by first and second stimulations was measured as indicated. Right panels: collected data. Paired-pulse facilitation, expressed as the ratio of second response to first response (ordinates), was strongly dependent on the interpulse interval (abscissae). The data are represented as the mean ± S.E.M. (A, $n = 7$; B, $n = 9$).

evokes significantly larger synaptic potentials than the first stimulation does. This phenomenon is termed 'paired-pulse facilitation' and is generally observed in peripheral and central nervous systems [1,4,12–14]. Since non-synaptic responses (e.g. the presynaptic fiber potential) are not facilitated by paired-pulse stimulation [4,14], paired-pulse facilitation can be considered to represent 'synaptic' processes. To determine if the BLA-evoked potentials represent synaptic responses, we examined changes of the P1 and P2 waves by paired-pulse stimulation. As shown in Fig. 5A and B, the P1 wave showed a characteristic facilitation by paired-pulse stimulation of the BLA. The facilitation of P1 wave was seen at interpulse intervals of 50–200 ms. On the other hand, the P2 wave was slightly facilitated only at an interpulse interval of 50 ms.

3.3. Are the BLA-evoked potentials independent of the PP pathway?

Thomas et al. [21] reported that single-pulse stimulation of the lateral amygdaloid nucleus evoked field potentials in the DG, which were abolished by injection of a local anesthetic procaine into the PP. This observation suggests that the lateral amygdaloid nucleus projects to the DG via a disynaptic pathway relaying in the entorhinal cortex. To determine if the BLA-evoked potentials are independent of the PP pathway, we carried out the following two experiments.

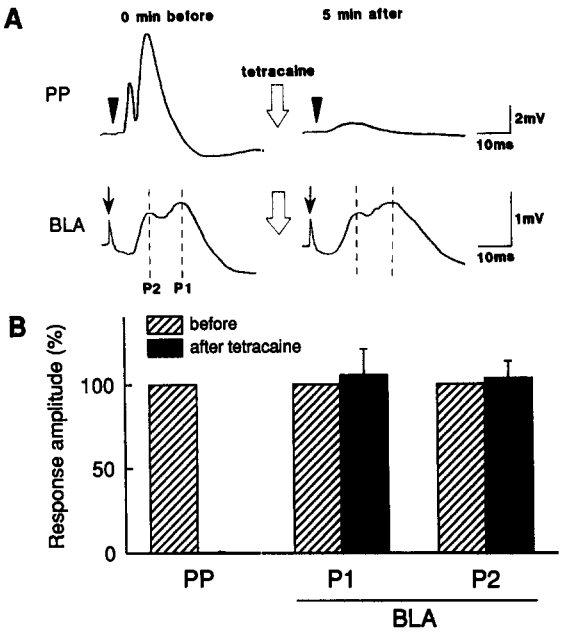

Fig. 6. BLA-evoked DG field potentials are not affected by tetracaine injection into the PP. Field potentials were evoked by single-pulse test stimulation (100 μA) of PP or BLA. A: representative records of PP- and BLA-evoked DG field potentials immediately before and 5 min after tetracaine injection. B: collected data with four rats. Changes in PP-evoked DG potentials were quantitated by measuring the population spike amplitude, and changes in BLA-evoked DG potentials were quantitated by measuring the peak amplitudes of P1 and P2 waves. The response amplitude 5 min after tetracaine injection into the PP (solid black columns) was expressed as a percentage of that immediately before the injection (shaded columns). The data are represented as the mean and S.E.M. ($n = 5$).

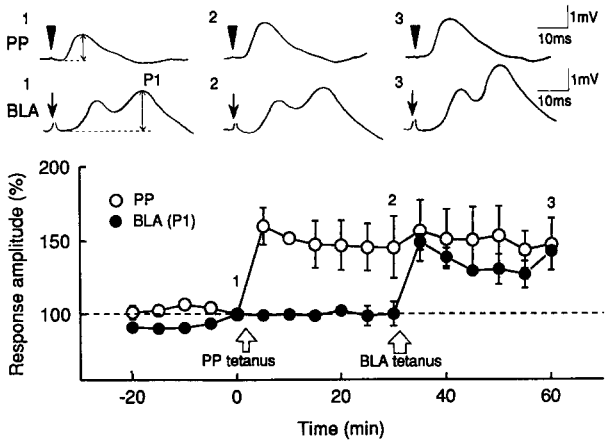

Fig. 7. DG response to BLA stimulation is specifically potentiated by tetanic stimulation of the BLA. DG responses to PP and BLA test stimulation were alternately recorded at intervals of 15 s. The intensity of PP test stimulation was set for a level (30–60 μA) which evoked half-maximum amplitude of EPSP wave. The intensity of BLA test stimulation was set for 100 μA. The time-course graph shows changes of PP- or BLA-evoked responses following tetanic stimulation of the PP or BLA. Amplitude of PP-evoked EPSP (open circles) and BLA-evoked P1 wave (filled circles) was expressed as a percentage of baseline value immediately before PP tetanic stimulation. The data are shown as the mean ± S.E.M. of 4 experiments. Above insets are representative records of PP- or BLA-evoked responses at the times denoted by the numbers.

First, we examined if the BLA-evoked potentials disappear when the PP is inactivated by a local anesthetic tetracaine. As shown in Fig. 6, the DG responses evoked by PP stimulation was completely abolished by injection of 100–200 nmol tetracaine into the PP, whereas the DG response to BLA stimulation was unaffected.

Second, we examined the effect of tetanic stimulation of the PP or BLA on the BLA-evoked potentials. LTP in the DG displays input specificity; when two independent sets of afferent fibers converging on a common populations of cells are stimulated, LTP is produced in responses to tetanized inputs but not in responses to nontetanized inputs [2,7]. If BLA stimulation elicited the DG field potentials by activating the PP, it could be expected that when LTP is induced in the PP-DG pathway, the BLA-evoked response is also potentiated. In Fig. 7, the PP and BLA were alternately stimulated in the same rat, and the evoked potentials were recorded with the same electrode positioned at DG granule cell layer. Tetanic stimulation of the PP (100 Hz for 1 s, twice at an interval of 30 s) produced robust LTP in the PP-DG pathway, but the BLA-evoked responses were not affected (Fig. 7). Furthermore, tetanic stimulation of the BLA (100 Hz for 1 s, twice at an interval of 30 s) did not potentiate the PP-evoked responses, but produced LTP of the BLA-evoked responses (Fig. 7).

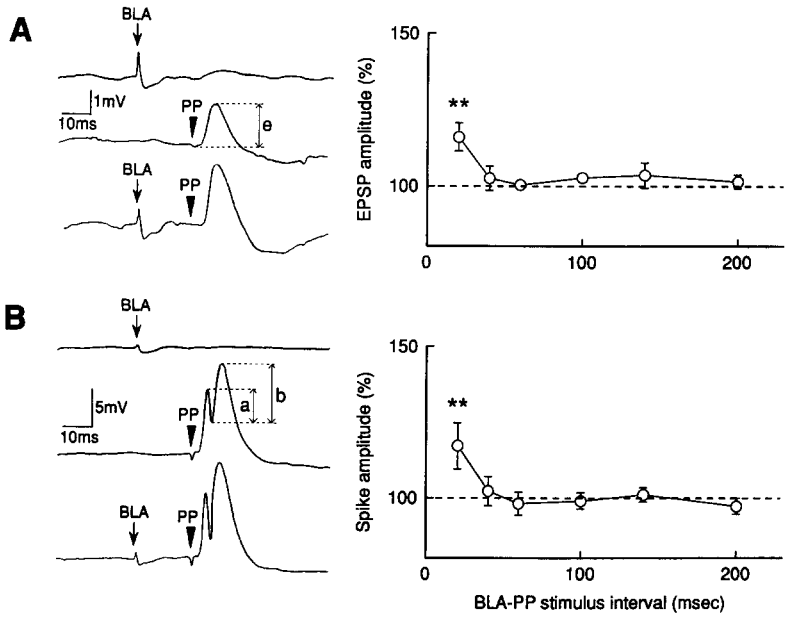

Fig. 8. Facilitation of the PP-DG synaptic responses by prestimulation of the BLA at a subthreshold level which alone evoked no or little response. A: the intensity of PP stimulation was set for a level which evoked half-maximum amplitude of EPSP, and the influence of BLA prestimulation on the PP-evoked EPSP component was examined. The PP-evoked EPSP amplitude was measured as e. B: the intensity of PP stimulation was set for a level which evoked half-maximum amplitude of population spike, and the influence of BLA prestimulation on the population spike component was examined. The PP-evoked population spike amplitude was measured as (a + b)/2. Left: sample records in which the BLA was stimulated 20 ms prior to the PP. Right: amplitude of the EPSP or population spike evoked by PP (test) stimulation following BLA (conditioning) stimulation was expressed as a percentage of the control response (no BLA prestimulation) and plotted as a function of the BLA-PP stimulus interval. The data are represented as the means and S.E.M. (A, $n = 7$; B, $n = 6$). ** $P < 0.01$, Duncan's multiple range test.

3.4. How does BLA prestimulation affect the PP-evoked response?

Finally, we investigated the influence of BLA stimulation on the PP-DG synaptic responses. When BLA stimulation (conditioning stimulation) was applied prior to PP stimulation (test stimulation), the response to PP stimulation was significantly facilitated. The magnitude of facilitation and the extent of the interpulse interval over which facilitation was observed depended on the intensity of

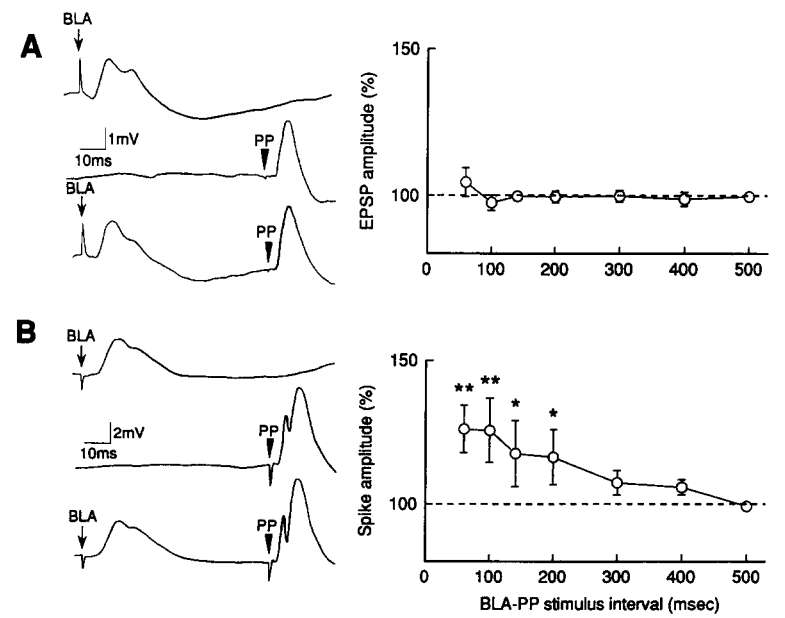

Fig. 9. Facilitation of the PP-DG potentials by prestimulation of the BLA at a high current level. Experimental protocol and representation of graphs are the same as in Fig. 7 except that the intensity of BLA stimulation was set for a level strong enough to evoke both P1 and P2 waves. In sample records, the BLA was stimulated 70 ms prior to the PP. The data are represented as the means and S.E.M. (A, $n = 7$; B, $n = 7$). * $P < 0.05$, ** $P < 0.01$, Duncan's multiple range test.

BLA stimulation. In Fig. 8, BLA stimulus intensity was set for a level which alone evoked no or little response. In this case, both EPSP and population spike of PP-evoked potentials were significantly facilitated when BLA stimulation was delivered 20 ms prior to PP stimulation. No facilitation was observed for longer (> 40 ms) interpulse intervals. In Fig. 9, BLA stimulus intensity was set for a level strong enough to evoke both P1 and P2 waves. Since superimposition of BLA-evoked waves makes it difficult to analyze changes of PP-evoked potentials, the interpulse interval was set for more than 50 ms. In this case, the BLA prestimulation produced facilitation of population spike, but not EPSP, of PP-evoked potentials, which was observed for interpulse intervals up to 300 ms.

4. Discussion

The DG field potentials evoked by BLA stimulation has not been described before. Therefore, we will first discuss what types of neuronal responses are represented by the evoked potentials. Secondly, the relationship between the BLA- and PP-evoked responses will be discussed.

4.1. Analysis of BLA-evoked DG field potentials

Ipsilateral BLA stimulation evokes two distinct components of field potentials in the DG. The P1 component with 26-ms peak latency is elicited by relatively low intensity of BLA stimulation. The following facts indicate that the P1 component represents synaptic responses of DG granule cells to neural inputs from the BLA: (1) P1 is elicited when the stimulating electrode is within the BLA; (2) P1 is observed as a positive wave in the DG granule cell layer and as a negative wave in the molecular layer, and is not recorded outside the DG; (3) P1 is strongly suppressed by prestimulation of the PP; and (4) P1 exhibits strong paired-pulse facilitation. It should be also noted that the latency of P1 wave is little shifted at increasing stimulus intensity. This property is typical for monosynaptic responses. On the other hand, P2 component with 14-ms peak latency is elicited at higher stimulus current levels. Since the P2 component is elicited even when the stimulating electrode is outside the BLA, it does not necessarily originate from the BLA. The fact that P2 wave does not reverse its polarity throughout the DG suggests that it may represent volume conducted from some other area of the brain. Taken together, it can be concluded that the P1 wave represents synaptic responses of DG granule cells to neural inputs from the BLA.

4.2. Relationship between BLA- and PP-evoked DG field potentials

The BLA-evoked DG field potentials are not affected by inactivation of the PP pathway and display LTP independently of the PP-evoked response. These facts suggest that neural inputs from the BLA are not mediated by the PP. The laminar profile of BLA-evoked potentials is similar to that of PP-evoked potentials, suggesting that neural projections from the BLA terminate in the DG molecular layer. However, further anatomical studies are necessary to identify the exact projection pathway from the BLA to the DG.

Furthermore, we observed a characteristic facilitation of the PP-DG synaptic responses by BLA prestimulation. Subthreshold BLA stimulation facilitates the PP-DG synaptic responses only when the stimulus interval is set for 20 ms. This facilitation probably reflects changes in synaptic mechanisms (increased release of neurotransmitters from presynaptic terminals or increased response of postsynaptic receptors), for both EPSP and population spike of the PP-evoked potentials are facilitated in a parallel manner. On the other hand, strong BLA stimulation produces facilitation of population spike of the PP-evoked potentials, which is observed for relatively longer interpulse intervals (50–300 ms). This facilitation probably reflects increased excitability of DG granule cells. We have previously found that the induction of LTP in PP-DG synapses is facilitated by BLA stimulation [10]. The facilitation of PP-DG synaptic responses by BLA stimulation may contribute to the facilitation of DG LTP by BLA neurons, although further investigations are necessary to clarify the cellular mechanisms.

4.3. Conclusion

In summary, we identified the field potentials that represent direct neural connections from the BLA to the DG. In addition, we found that the BLA-DG synapses display LTP independently of the PP pathways. This novel form of LTP may be a useful model for studying cellular mechanisms which associate 'emotion' and 'memory'.

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