



Stimulus intensity-dependent modulations of hippocampal long-term potentiation by basolateral amygdala priming

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There is growing realization that the relationship between memory and stress/emotionality is complicated, and may include both memory enhancing and memory impairing aspects. It has been suggested that the underlying mechanisms involve amygdala modulation of hippocampal synaptic plasticity, such as long-term potentiation (LTP). We recently reported that while in CA1 basolateral amygdala (BLA) priming impaired theta stimulation induced LTP, it enhanced LTP in the dentate gyrus (DG). However, emotional and stressful experiences were found to activate synaptic plasticity within the BLA, raising the possibility that BLA modulation of other brain regions may be altered as well, as it may depend on the way the BLA is activated or is responding. In previous studies BLA priming stimulation was relatively weak (1 V, 50 μ s pulse duration). In the present study we assessed the effects of two stronger levels of BLA priming stimulation (1 V or 2 V, 100 μ s pulse duration) on LTP induction in hippocampal DG and CA1, in anesthetized rats. Results show that 1V-BLA priming stimulation enhanced but 2V-BLA priming stimulation impaired DG LTP; however, both levels of BLA priming stimulation impaired CA1 LTP, suggesting that modulation of hippocampal synaptic plasticity by amygdala is dependent on the degree of amygdala activation. These findings suggest that plasticity-induced within the amygdala, by stressful experiences induces a form of metaplasticity that would alter the way the amygdala may modulate memory-related processes in other brain areas, such as the hippocampus.

Keywords: emotional memory, plasticity, stress, limbic system, amygdala, rat

INTRODUCTION

It is generally accepted that memory is organized in multiple brain systems that can functionally interact with each other (Squire and Zola, 1996; Thompson and Kim, 1996). Two of these specialized systems are the hippocampus, which is crucial for associative type (Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Morris, 2001; Day et al., 2003) and other types of learning and memory (Morris et al., 1982; Eichenbaum et al., 1996; Squire and Zola, 1996; Abrahams et al., 1999), and the amygdala, which plays a pivotal role in mediating many aspects of the stress response, fear-motivated learning, and memory for emotionally evocative events (LeDoux, 2000, 2003; McGaugh, 2004; Berretta, 2005). It has been suggested that emotional arousal/stress activates the amygdala and that this activation, specifically that of the basolateral amygdala (BLA), results in modulation of memory-related processes in the hippocampus (McGaugh, 2000; Richter-Levin and Akirav, 2000; Roozendaal, 2000; Packard and Cahill, 2001; Richter-Levin, 2004; LaBar and Cabeza, 2006). Thus, these two structures form a functional system relevant to the complicated effects of emotionality and stress on learning and memory (Kim and Diamond, 2002; Roozendaal, 2002; Prickaerts and Steckler, 2005; Lupien et al., 2007). On the one hand, considerable research shows that the interactions between amygdala and hippocampus are necessary for the enhanced encoding and consolidation of memory for

emotionally arousing material and contexts (Cahill, 2000; Canli et al., 2000; Packard and Cahill, 2001; Phelps, 2004; Phelps and LeDoux, 2005). On the other hand, amygdala activation is suggested to mediate stress-induced impairment of hippocampus-dependent memory (Akirav and Richter-Levin, 2006; Hurlmann et al., 2007a,b; Maroun and Akirav, 2008).

Consistent with the complex relationship between stress and memory, stress can differently influence synaptic plasticity, such as long-term potentiation (LTP) (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Martin et al., 2000; Malenka and Bear, 2004). In the hippocampus, data so far suggest differential susceptibility to stressful events in its different subregions. Extensive observations from *in vitro* and *in vivo* electrophysiological studies indicate that variant stress paradigms, including unpredictable and inescapable restraint-tail shock (Foy et al., 1987; Kim et al., 1996; Garcia et al., 1997; Shors et al., 1997) or footshock (Shors et al., 1989; Li et al., 2005), forced exposure to brightly lit and unfamiliar chambers (Diamond et al., 1990; Xu et al., 1997), unavoidable exposure to a predator (Mesches et al., 1999), or platform stress (Maroun and Richter-Levin, 2003), discriminatory avoidance learning (Izaki and Arita, 1996), as well as contextual fear conditioning (Sacchetti et al., 2002; Hirata et al., 2009), all impaired LTP in the CA1. However, different stressors were reported to either impair (Diamond and Rose, 1994; Shors and

Dryver, 1994; Wang et al., 2000; Korz and Frey, 2005; Ahmed et al., 2006), enhance (Izaki and Arita, 1996; Gerges et al., 2001; Kavushansky et al., 2006; Spyrka and Hess, 2010), or have no effect (Bramham et al., 1998; Garcia, 2001; Gerges et al., 2001; Pavlides et al., 2002; Yamada et al., 2003; Vouimba et al., 2004; Yarom et al., 2008) on the ability to induce LTP in the DG. Furthermore, Korz and Frey (2003) reported a bidirectional effect of behavioral stress on the maintenance of DG-LTP, i.e., handling 15 min after the induction of early LTP resulted in an impairment of LTP, whereas a 2 min swim also 15 min after induction resulted in prolongation of LTP up to 24 h (Korz and Frey, 2003). Given critical role of amygdala in stress, one can suggest a possible way to explain complex effects of stress on hippocampus-dependent learning and memory that invokes differential effects of stressors on amygdala action, which in turn results in differential effects on LTP in different subregions of the hippocampus (Tsoory et al., 2008).

Indeed, the amygdala is critical in the modulation of hippocampal synaptic plasticity. Lesions of amygdala or pharmacological intervention of its function effectively prevented the effects of stress on hippocampal CA1 LTP, as well as on hippocampus-dependent spatial and fear memory (Kim et al., 2001, 2005; Goosens and Maren, 2004; Yang et al., 2008). Also, the behavioral or motivational reinforcement of hippocampal DG LTP (that can transform early LTP into late LTP) are reported to depend on the function of the amygdala (Almaguer-Melian et al., 2003; Korz and Frey, 2005). Consistently, hippocampus DG/CA1 LTP can be modulated by electrical stimulation of the amygdala (Akirav and Richter-Levin, 1999a,b; Abe, 2001; Frey et al., 2001; Akirav and Richter-Levin, 2002; Nakao et al., 2004; Vouimba and Richter-Levin, 2005; Vouimba et al., 2007). However, the profiles of amygdala modulation of hippocampal LTP are intriguing. Thus, while BLA lesions or its pharmacological suppression were reported to impair *in vivo* LTP of perforant path (PP)-DG (Abe, 2001), Korz and Frey (2005) reported facilitation of DG LTP in BLA lesioned animals (Korz and Frey, 2005). Similarly, BLA stimulation was reported to augment LTP in PP-DG pathway (Ikegaya et al., 1995, 1996; Akirav and Richter-Levin, 1999a; Frey et al., 2001), whereas later reports demonstrated that this effect vary considerably depending on the interplay of the strengths and timing of BLA and PP stimulation (Akirav and Richter-Levin, 1999b; Nakao et al., 2004; Vouimba and Richter-Levin, 2005). For example, although it was reported that BLA stimulation only affects weak and transient forms of LTP and LTP produced by a strong tetanus does not require the BLA for its induction nor its maintenance (Ikegaya et al., 1995; Frey et al., 2001), our previous series of results showed that BLA activation, applied 30s before or 1–2 h after strong tetanus application, could enhance or impair DG LTP induced by a strong tetanus, respectively, (Akirav and Richter-Levin, 1999a,b, 2002). Furthermore, consistent with our previous findings, we have recently showed that BLA activation (applied 30 s prior to or after the presentation of stimulation tetanus) impairs CA1 LTP in response to weak tetanus but enhances DG LTP in response to both weak and strong tetanus (Vouimba and Richter-Levin, 2005). Thus, we have suggested that, depending on how the amygdala is

activated in terms of intensity, timing relationship, duration, and contextual input during information processing, the hippocampal outcome would involve the components of both/either enhancing and/or suppressing effects (Akirav and Richter-Levin, 2006; Tsoory et al., 2008), possibly providing synaptic plasticity mechanism underlying manifold/heterogeneous effects of stress on memory.

The present study was undertaken to further characterize the intriguing profiles of modulation of hippocampal synaptic plasticity by amygdala in order to elaborate on the mechanisms underlying the complex stress-memory relationship. We have previously demonstrated that relatively weak BLA activation 30 s prior to LTP induction in the hippocampus enhanced theta stimulation-induced LTP in DG, but decreased LTP in CA1 of the hippocampus (Vouimba and Richter-Levin, 2005). Here, we assessed the effects of two stronger levels of BLA priming stimulation on LTP, induced in hippocampal dentate gyrus (DG) and CA1 subregions in the anesthetized rat. The results demonstrate that BLA priming differently modulates subsequent LTP in the hippocampus depending on the degree of BLA activation.

MATERIALS AND METHODS

SUBJECTS

The experiments were performed using male Sprague–Dawley rats (Harlan Laboratories, Jerusalem, Israel) weighing 270–340 g. Rats were housed in Plexiglas cages (six rats per cage) and were maintained on a free-feeding regimen with a 12:12 h light/dark schedule. All electrophysiological testing was performed at least 1 week after their arrival, during the light phase of the cycle. During the course of the experiment, body temperature was monitored and maintained at $37 \pm 0.5^\circ\text{C}$ using a regulated heating pad.

All procedures and tests were approved by the Institutional Animal Care Committee and adhered to the guidelines of the NIH Guide for the Care and Use of Laboratory Animals.

ELECTROPHYSIOLOGY

Surgery

Rats were anesthetized (40% urethane +5% chloral hydrate, 0.5 ml/100 g, i.p.) and mounted on a stereotaxic frame (Stolting, Wood Dale, IL). The scalp was incised and retracted, and the head position was adjusted to place bregma and lambda in the same horizontal plane. Small burr holes (1.5–2 mm diameter) were drilled in the skull for the placement of stimulating and recording electrodes. A reference electrode consisting of a 125 μm coated wire was affixed to the skull in the area overlapping the nasal sinus. A recording glass electrode (tip diameter, 2–5 μm ; filled with 2 M NaCl) was stereotaxically positioned in the CA1 pyramidal cell layer [4.0 mm posterior to bregma (AP), 2.5 mm from midline (ML) and ~ 2 mm dorsoventral (DV) from dura] or in the DG granular cell layer (4.0 mm AP, 2.5 mm ML and 2.7–3.0 mm DV from dura). Bipolar concentric stimulating electrodes (125 μm ; Kopf, Tujunga, CA) were inserted in the ipsilateral BLA (2.8 mm AP, 4.8 mm ML, and 7.6 mm DV) and either in the contralateral ventral hippocampal commissure (vHC: 2 mm AP, 1.5 mm ML, and ~ 3 mm DV from dura) for activating field potentials in the CA1 or in the ipsilateral perforant path (PP: 8 mm AP, 4.0 mm ML, and 2.5–3.0 mm DV from dura) for

activating field potentials in the DG. The DV location of the recording and stimulating electrodes was adjusted to maximize the amplitude of evoked field potentials.

Stimulating and recording procedures

CA1 and DG field potentials evoked by single pulses delivered to the vHC or PP, respectively, (0.1 ms rectangular monophasic pulses) were amplified ($\times 1000$) (AM-Systems amplifier), displayed on an oscilloscope, digitized at 10 kHz (CED) and stored to disk for off-line analysis (Spike-2 software). Baseline responses were established by means of a stimulation intensity sufficient to elicit a response representing 20–40% of the maximal amplitude of the evoked-field potentials. LTP was assessed by measuring both the increase in the population spike amplitude (PS) and the slope of the excitatory postsynaptic potential (EPSP) component, for the DG. However, in CA1, because of the early occurrence of the PS in some recordings, the slope was not measurable and, therefore, only the PS was analyzed and reported here. In our previous study (Vouimba and Richter-Levin, 2005) we have shown that both the PS and the slope of the EPSP (for both DG and CA1) follow the same pattern of changes responding to theta stimulation and amygdala modulation.

Protocols

Stable baseline recording of evoked-field potential in DG or CA1 was established for 30 min (1 pulse every 15 s) for all groups [For both DG and CA1: Control (electrode placed in the BLA but not stimulated), BLA Priming (1 V), and BLA Priming (2 V)]. Following baseline recording, LTP was induced by moderate theta burst stimulation (mTS: 10 trains, each consisting of 10 pulses at 100 Hz, with an intertrain interval of 200 ms; with trains delivered at test stimulus intensity) relative to our previously used strong TS (three sets of 10 trains; each train consisted of 10 pulses at 100 Hz, with an intertrain interval of 200 ms and an interset interval of 1 min) and weak TS (one set of five trains, each train consisting of five pulses at 100 Hz, with an inter-train interval of 200 ms) to the PP or vHC (Akirav and Richter-Levin, 1999a,b, 2002; Vouimba and Richter-Levin, 2005; Vouimba et al., 2007). After mTS stimulation, responses to test pulse stimuli were recorded every 15 s for 1 h. The BLA Priming groups received a priming stimulation of BLA (1 V or 2 V, 100 μ s pulse duration, 10 trains of five pulses at 100 Hz; intertrain interval, 200 ms) 30 s before mTS to the PP or vHC was applied. The 1 V BLA priming stimulation (1 V, 50 μ s pulse duration, 10 trains of five pulses at 100 Hz; intertrain interval, 200 ms) used in a previous study (Vouimba et al., 2007) had no significant effects on EPSP slope while having a small but significant effect on PS in DG when compared with the naive control; however, it had no effects on both EPSP slope and PS in CA1. In a pilot experiment for the current study, both BLA priming stimuli had no significant effects on EPSP slope in DG of the three tested groups (the two BLA priming groups and the naive control group); the 1 V BLA priming stimulus resulted in a small but significant increase of PS in DG compared with the naive control group, as was found in our previous study. The other stimulus intensity (2 V) had a small but not significant effect on DG PS and there was no significant

difference between the two BLA priming groups. The two intensities of BLA priming stimuli had no effects on EPSP slope or PS in CA1. In addition, at both stimulus intensities, there were no visible responses in DG/CA1 in response to single stimulation pulses to the BLA. The Control animals were implanted in the BLA with stimulating electrodes through which no priming stimulation of BLA was applied.

HISTOLOGY

After completion of the electrophysiological examination of the recording in DG or CA1, electrical lesions of BLA were made by passing anodal current in stimulating electrodes in BLA group animals (5 mV DC for 20 s), not including the control animals with BLA stimulating electrodes through which no stimulation was given. Animals were then decapitated and their brains were frozen at -80°C for further analysis. Coronal sections (60 μ m) were cut using LEICA cryostat, and mounted on glass microscope slides. Sections were stained with Cresyl violet. The stimulating electrodes placements were verified under microscopic examination according to the atlas (Paxinos and Watson, 1997).

STATISTICS

The amplitude of the PS and the slope of the EPSP were expressed as the mean percentage (\pm SEM) of the individual basal values of animals for each group. Only the animals that had correct positions of the stimulating electrodes in the BLA, according to the histology, were included in the analysis. Student's paired *t*-test was used to decide whether or not LTP was induced after TBS in each group. ANOVA for repeated measures with least significant difference test (LSD) as *post-hoc* test was used to compare LTP between groups. Statistical significance was set at $P < 0.05$.

RESULTS

HISTOLOGY

Figure 1 illustrates the location of stimulating electrode site in BLA. Histological analysis revealed that near 90% of rats recorded had correct positions of the stimulating electrodes in the BLA. Only data from these subjects was used in the analysis.

EFFECTS OF BLA ACTIVATION ON LTP-INDUCED BY MTS IN CA1 AND THE DG

Paired *t*-test revealed that in all the groups mTS reliably induced LTP of PS and slope in DG and LTP of PS in CA1 [*t*-tests for difference from baseline (100%) at 60 min after mTS. PS amplitude/EPSP slope in DG: Control group (201% of baseline, $t_8 = -6.3$, $P < 0.001$)/(123% of baseline, $t_8 = -8.8$, $P < 0.01$); 1V-BLA priming group (274% of baseline, $t_8 = -12.3$, $P < 0.001$)/(134% of baseline, $t_8 = -10.4$, $P < 0.001$); 2V-BLA priming group (157% of baseline, $t_9 = -3.7$, $P < 0.01$)/(114% of baseline, $t_9 = -6.0$, $P < 0.001$). PS amplitude in CA1: Control group (415.5% of baseline, $t_6 = -3.8$, $P < 0.01$); 1V-BLA priming group (243% of baseline, $t_6 = -5.7$, $P < 0.005$); 2V-BLA priming group (238% of baseline, $t_6 = 4.5$, $P < 0.005$). See **Figures 2A,C** and **3A**]. ANOVA analysis conducted on both DG LTP and CA1 LTP at different time points [groups \times time

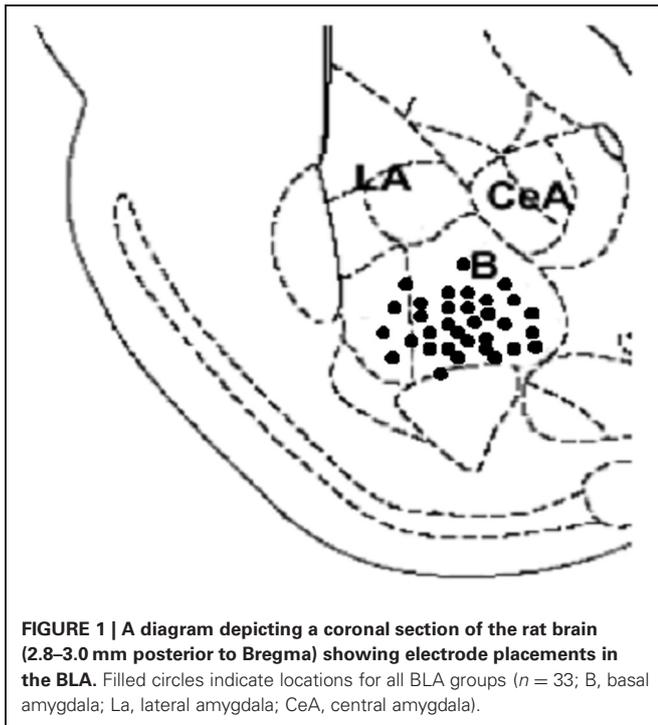


FIGURE 1 | A diagram depicting a coronal section of the rat brain (2.8–3.0 mm posterior to Bregma) showing electrode placements in the BLA. Filled circles indicate locations for all BLA groups ($n = 33$; B, basal amygdala; La, lateral amygdala; CeA, central amygdala).

(3×12) revealed significant difference between the groups (Control group, 1V-BLA priming group and 2V-BLA priming group) [PS amplitude/EPSPs slope in DG: $F(2, 25) = 9.96$, $P < 0.005$ / $F(2, 25) = 5.41$, $P < 0.02$; PS amplitude in CA1: $F(2, 18) = 3.858$, $P < 0.05$. See **Figures 2A,C** and **3A**].

In DG, 1V-BLA priming (30 s prior to application of mTS to PP-DG) enhanced LTP compared with Control, showing significantly greater PS-LTP at all time points post-mTS ($P_s < 0.05$; See **Figure 2B**) and significantly greater slope-LTP at the last two 10 min-period blocks ($P_s < 0.05$; See **Figure 2D**). In contrast, 2V-BLA priming (30 s prior to application of mTS to PP-DG) impaired LTP of PS compared with Control, showing significantly smaller PS-LTP ($P < 0.05$; See **Figure 2B**) and significantly smaller slope-LTP ($P < 0.05$; see **Figure 2D**) at the last 10 min-period block post-mTS. Comparison between the two levels of BLA priming activation demonstrated that LTP in DG induced by mTS following 1V-BLA priming activation was significantly different from that induced by mTS following 2V-BLA priming activation for PS at time points post-mTS ($P_s < 0.01$; See **Figure 2B**) and for slope at all time points post-mTS except the first initial 10 min ($P_s < 0.05$; See **Figure 2D**).

In contrast, in CA1, the response to BLA priming activation was quite different. In comparison to Control, both levels of BLA priming (30 s prior to application of mTS to vHC-CA1) similarly impaired PS-LTP (1V-BLA priming vs. 2V-BLA priming, $P_s > 0.05$; see **Figure 3**), with 2V-BLA priming activation significantly inhibiting PS-LTP in CA1 at all time points post-mTS (compared with Control, $P_s < 0.05$. see **Figure 3B**) and 1V-BLA priming activation significantly inhibiting PS-LTP in CA1 at the last two 10 min-period blocks post-mTS (compared with Control, $P_s < 0.05$. see **Figure 3B**). Thus, BLA activation

differentially modulated hippocampal plasticity, depending on both hippocampal subregions and the degree of BLA activation. **Figure 4** showed representative analog traces for baseline and the last 10 min-period block post-mTS from Control and BLA priming groups.

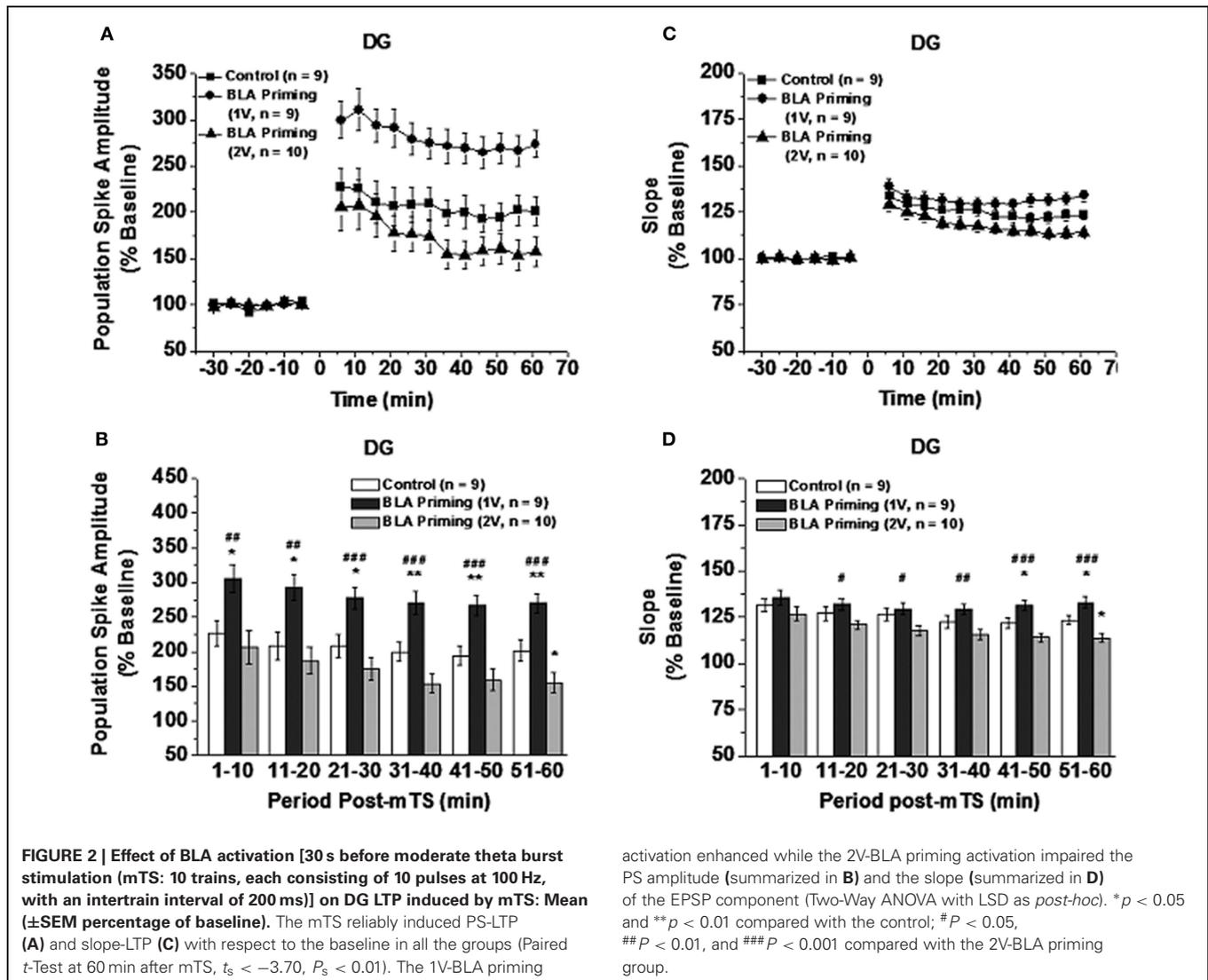
DISCUSSION

We examined the effects of two levels of BLA priming activation on synaptic plasticity in the PP input to the granule cells in the DG, and the vHC input to the CA1 pyramidal cells of the hippocampus. The results show that 1V-BLA priming stimulation enhanced but 2V-BLA priming stimulation impaired DG LTP, whereas both levels of BLA priming stimulation impaired CA1 LTP. These results suggest that amygdala modulation of hippocampal synaptic plasticity is dependent both on the degree of amygdala activation and on hippocampus subregion examined.

We previously found that employing a similar pattern of amygdala priming but with a shorter pulse duration (50 μ s) (weaker priming) enhanced PP-DG LTP induction (Akirav and Richter-Levin, 1999a,b, 2002; Vouimba and Richter-Levin, 2005; Vouimba et al., 2007). Our current results with 1V-BLA priming are consistent with those findings. However, further strengthening BLA priming intensity (2 V, 100 μ s pulse duration) did not further enhance, but on the contrary inhibited DG LTP, suggesting that different degrees of BLA activation may exert bidirectional influence on synaptic plasticity in the DG. Nakao et al. (2004) reported that the effects of amygdala activation on DG synaptic plasticity could range from LTP to LTD depending on the degree and timing of neural activity of the BLA. They showed that strong BLA activation decreased the LTP-LTD crossover threshold to favor LTP, whereas weak BLA activation increased it. Beyond possible differences in the exact parameters/patterns of the BLA and PP stimulation between the two studies, there might exist an inverted U-shape function between the degree of BLA activation and its effects on the DG LTP, resembling that of glucocorticoid-hippocampal LTP relationship (De Kloet, 2004). In any case, the results demonstrate that BLA activation may result in enhancing or suppressing effects on DG-LTP, depending on the exact parameters of BLA activation.

In contrast, in the vHC-CA1 pathway, both 1V-BLA priming and 2V-BLA priming impaired vHC-CA1 LTP. These results are in agreement with previous findings demonstrating that relative weak BLA priming activation attenuated the LTP induction in this pathway (Vouimba and Richter-Levin, 2005; Vouimba et al., 2007). Together, the results suggest that LTP in CA1 is more susceptible to interference by amygdala activation compared with DG.

Stress hormones, glucocorticoids (GC), and noradrenaline (NA) with their synergistic interaction in the BLA are suggested to mediate negative and positive influence on memory by emotion or stress (McGaugh, 2000; Lupien et al., 2007; Hurlmann et al., 2007a,b), and thus could be implicated in the underlying mechanism of our present findings. In support of this, we have previously demonstrated that BLA stimulation effects on DG-LTP involve both NA and GC (Akirav and Richter-Levin, 2002; Vouimba et al., 2007). Furthermore, despite that NA and β -adrenergic stimulation has been shown repeatedly to be involved

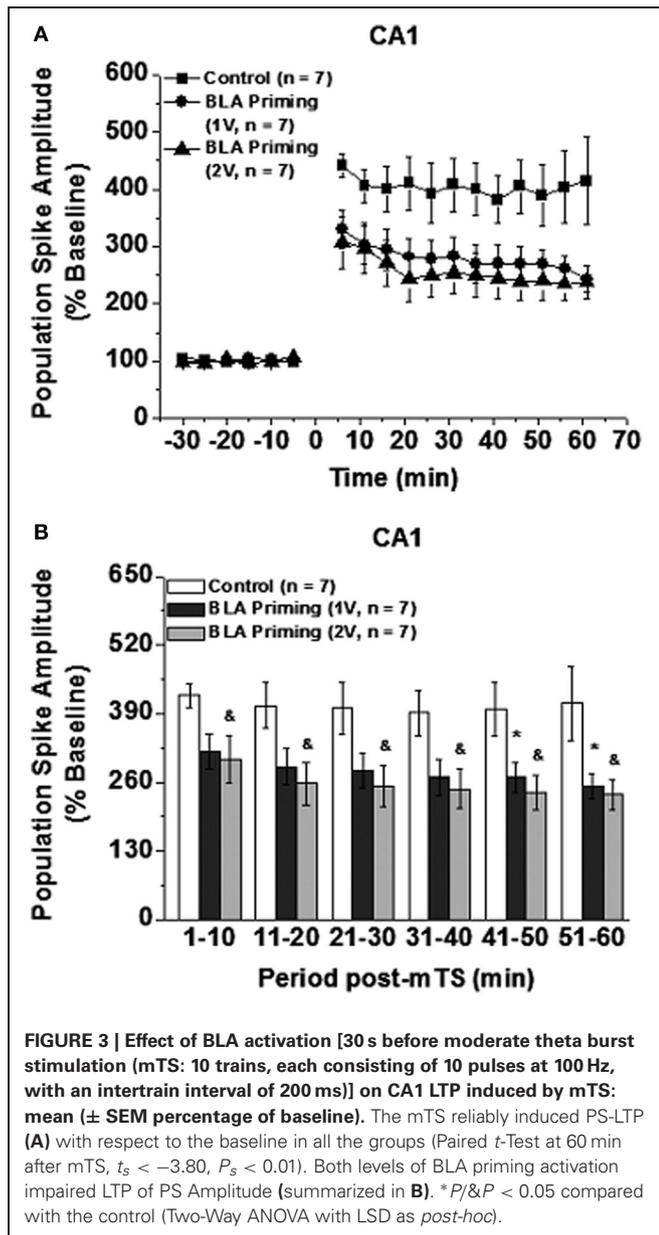


in the reinforcement of hippocampal LTP (Izquierdo and Medina, 1995; Thomas et al., 1996; Katsuki et al., 1997; Seidenbecher et al., 1997; Watabe et al., 2000; Gelinan and Nguyen, 2005), recent studies showed that low doses of NA (administered icv) effectively reinforced DG LTP while a higher dose was not effective (Almaguer-Melian et al., 2005). Systematically administered adrenaline enhanced DG LTP in an inverted-U dose-response function (Korol and Gold, 2008), possibly by causing NA release in many brain regions such as hippocampus and amygdala (Gold and van Buskirk, 1978; Williams et al., 1998; Miyashita and Williams, 2004). In contrast to DG LTP, BLA priming effects on CA1 LTP were not affected by blockade of NA or GC activation in BLA (Vouimba et al., 2007), suggesting that the mediating mechanisms of effects differ between CA1 and DG.

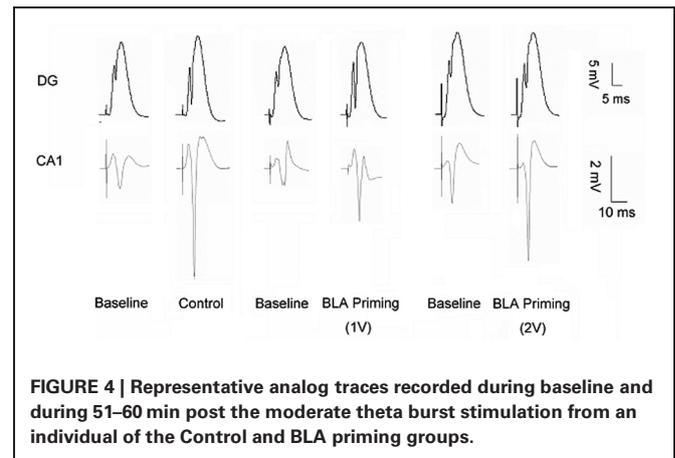
On the other hand, connected with stress and stress hormones such as NA showing to activate the amygdala in both humans and animals (Pelletier et al., 2005; Buffalari and Grace, 2009; Roozendaal et al., 2009; van Marle et al., 2009), different stressors may affect amygdala activity in different ways (Roozendaal

et al., 2009). For example, Hand et al. (2002) have demonstrated differential release of corticotropin-releasing hormone (CRH) in the amygdala during different types of stressors. The level of activation of the MAP Kinase cascade in the BLA was also found to depend on the level of stress involved (Kogan and Richter-Levin, 2008; Ilin and Richter-Levin, 2009). Furthermore, activity in the BLA was found to be enhanced by the application of corticosterone in a dose-dependent manner (Kavushansky and Richter-Levin, 2006). These phenomena support the notion that different patterns of BLA stimulation mimic effects of different stressor-induced alterations in amygdala activation, and such alterations, as indeed demonstrated here, modulate the way the amygdala influences activity and plasticity in other brain regions, such as memory-related processes in hippocampus (Tsoory et al., 2008; Roozendaal et al., 2009).

The amygdala is a pivotal structure associated with stress. It has been suggested before that stress exerts its effects on brain regions, such as the hippocampus, at least partially by activating the BLA (for review: Richter-Levin, 2004 or Tsoory et al., 2008).



For example, BLA activation induces an increase in serum corticosterone (Rubin et al., 1966; Feldman et al., 1982; Dunn and Orr, 1984). In a recent study (Vouimba et al., 2007), we found that the 1V BLA priming stimulation protocol increased serum corticosterone levels to a lower level than that induced by swim stress in a platform-deprived water maze (Kavushansky et al., 2006), though both of these studies showed enhanced LTP in DG and impaired LTP in CA1. However, stronger BLA priming (2V) was found in the present study to impair both DG-LTP and CA1-LTP. This is in agreement with previous findings indicating that while water maze exposure stress enhances DG-LTP (Kavushansky et al., 2006), under-water trauma, which is considered to be a more intense stressor, blocked DG-LTP (Wang et al., 2000). Together, these results indicate that different patterns



of BLA priming are likely to reflect specific amygdala activation states by different stressors.

Interestingly, it has been demonstrated that the exposure to a stressor may induce a form of metaplasticity that would affect the ability of a following stressor or of following BLA priming to modulate plasticity in other brain areas (Richter-Levin and Maroun, 2010). In relation to that Vouimba et al. (2004) found that while a single exposure to an elevated platform stress did not prevent LTP induction in the DG, it did induce a form of metaplasticity, since a repeated exposure to a similar stressor did suppress DG LTP. Thus, exposure to stress (Vouimba et al., 2004; Richter-Levin and Maroun, 2010) and amygdala priming (Richter-Levin and Maroun, 2010) were found to induce a form of metaplasticity that affects the ability of a following stress or following amygdala priming to modulate plasticity in other brain areas.

The current results further demonstrate that the BLA modulates synaptic plasticity in the hippocampus in a region-specific way (Vouimba and Richter-Levin, 2005; Vouimba et al., 2007). The nature of effects of BLA on synaptic plasticity differed between CA1 and the DG, such that in CA1 BLA activation impaired LTP, with stronger effects for stronger activation of the BLA, while in DG different stimulus intensities to the BLA resulted in differential effects on DG-LTP; a weak BLA stimulation enhanced DG-LTP but strong BLA stimulation impaired it. These results resemble those found following variant stressors, with a wide range of stressors found to suppress LTP in CA1 while different stressors found to affect DG-LTP on a spectrum from enhancement to impairment. Taken together, these findings lend further support to the notion that the BLA mediates some of the effects of stress and emotionality on hippocampal functioning (Richter-Levin, 2004).

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