ABSTRACT—Why are emotionally arousing experiences well-remembered? Since the amygdala and hippocampus play pivotal roles in emotion and memory, respectively, the interaction between these brain regions may underlie the formation of enhanced memory for emotionally arousing events. Behavioral experiments using animals have demonstrated that lesions of the amygdaloid nuclei or infusions of drugs into the amygdaloid nuclei impair or enhance hippocampal-dependent learning. In addition, we have obtained direct evidence that neural inputs from the amygdala modulate synaptic plasticity in the hippocampus, through electrophysiological experiments using anesthetized rats. Electrical stimulation of the basolateral amygdala evoked synaptic potentials in the dentate gyrus of the hippocampus, indicating that there is a neural connection from the amygdala to the hippocampus. Lesion of the basolateral or basomedial, but not central, amygdala resulted in attenuation of long-term potentiation (LTP) at the perforant path-dentate gyrus granule cell synapses. High-frequency stimulation of the basolateral or basomedial amygdala alone did not induce LTP in the dentate gyrus, but facilitated the induction of LTP when applied at the same time as tetanic stimulation of the perforant path. The activity-dependent facilitation of hippocampal LTP by the basomedial and basolateral amygdala may be a synaptic mechanism underlying memory enhancement associated with emotions.

Keywords: Amygdala, Hippocampus, Long-term potentiation, Emotion, Memory
Amygdala Modulates Hippocampal LTP

3. Neural projection from the amygdala to the hippocampus

Single-pulse electrical stimulation of the amygdala evoked synaptic potentials in the dentate gyrus of the hippocampus, and the dentate gyrus response to perforant path stimulation was enhanced by the preceding stimulation of the amygdala (6). We have also found that electrical stimulation of the BLA evoked synaptic potentials in the dentate gyrus of anesthetized rats (7). Evoked potentials in the dentate gyrus exhibited a long-lasting potentiation following amygdala stimulation (8). Injection of the excitatory amino acid N-methyl-D-aspartate (NMDA) into the amygdala induced c-fos expression in the ipsilateral dentate gyrus of the hippocampus (9). These observations support that there is neural projection from the amygdala to the hippocampus.

4. Hippocampal long-term potentiation

Hebb (10) proposed that memory is formed by a plastic change in synaptic functions, depending on neuronal activity. The input of stronger information may increase the efficiency of neurotransmission at specific synapses. Indeed, Bliss and Lømo (11) performed an electrophysiological experiment using anesthetized rabbits and demonstrated that application of high-frequency stimulation to presynaptic fibers in the hippocampus produced a long-lasting increase in postsynaptic potentials. This phenomenon was termed ‘long-term potentiation’ (LTP). Although LTP has been found in various brain regions including the visual cortex and amygdala, it should be noted that LTP is induced most easily and reproducibly in the hippocampus.

It is still unknown whether or not the LTP-like phenomenon really occurs when memory is formed in the brain. Experimentally, LTP is induced by applying artificial electrical stimulation to certain brain synapses. However, several lines of evidence support the view that LTP in the hippocampus is related to learning and memory: 1) learning behaviors of experimental animals were impaired by treatments that inhibit the induction of hippocampal LTP (12–14); 2) electrical stimulation inducing hippocampal LTP affected the acquisition of memory (15–17); 3) there was a correlation between learning ability and LTP induction (18–20). Hippocampal LTP has been extensively studied as a candidate mechanism underlying memory formation, although there are a number of observations showing dissociation between LTP and memory (21–23).

5. Modulation of hippocampal LTP by BLA and BMA

To test the possibility that neural inputs from the amygdala modulate synaptic plasticity in the hippocampus, we investigated the effects of lesions of several amygdaloid nuclei on the induction of LTP at the perforant path-dentate gyrus granule cell synapses of anesthetized rats in vivo. The dentate gyrus field potentials evoked by low-frequency test stimulation of the perforant path was not changed by lesions of any of the amygdaloid nuclei (24, 25). The magnitude of LTP following application of tetanic stimulation in ipsilateral BLA-lesioned rats was significantly smaller than that in intact or sham-operated rats (24). Similarly, dentate gyrus LTP was attenuated by lesion of the ipsilateral BMA (25). Lesion of the contralateral BLA or BMA had no effect on the induction of LTP (24, 25), consistent with the fact that a neural connection from the BLA...
or BMA to the DG is unilateral and ipsilateral (7). However, lesion of the CeA or MeA had no effect on the induction of LTP in the dentate gyrus (24, 25). These results suggest that, among the amygdaloid nuclei, the BLA and BMA play roles in modulation of hippocampal plasticity.

If the presynaptic axons are acutely transected, the propagation of the spontaneous firing signal originating in the soma of presynaptic neurons will be completely cut off, but the presynaptic nerve endings will retain the capability of releasing the neurotransmitter. Acute lesion of the BLA or BMA as well as chronic lesion was sufficient to cause the impairment of hippocampal LTP (24, 25), implying that modulation of dentate gyrus LTP by inputs from the BLA and BMA requires the propagation of amygdaloid neuron activity rather than the basal release of neurotransmitters from the nerve endings. There is evidence that the amygdaloid neurons are firing spontaneously (26, 27). Furthermore, inactivation of BLA neuron activity by the local anesthetic tetracaine resulted in attenuation of dentate gyrus LTP as effectively as BLA lesion (28). In addition, the induction of LTP in the dentate gyrus was partially impaired by injection of the NMDA receptor antagonist 2-amino-5-phosphonovalerate (29) or the β-adrenoceptor antagonist propranolol into the BLA (30). These results suggest that glutamatergic or β-adrenergic neuron activity in the BLA plays a critical role in modulation of hippocampal LTP.

BLA or BMA lesion, when made after perforant path tetanic stimulation, did not affect the established LTP in the dentate gyrus (24, 25). Similarly, injection of tetracaine into the BLA did not affect the maintenance phase of LTP (28). BMA and BLA neuron activities may be unnecessary once LTP has been established.

The role of the BMA and BLA in the induction of dentate gyrus LTP was further investigated by examining the effects of electrical stimulation of these amygdaloid nuclei. High-frequency stimulation of the ipsilateral BLA or BMA alone did not produce dentate gyrus LTP, but facilitated the induction of dentate gyrus LTP when coupled with weak tetanic stimulation of the perforant path (25, 31). BLA and BMA neurons facilitate potentiation at active, but not quiescent, hippocampal synapses. Furthermore, LTP induced by strong tetanic stimulation of the perforant path was not further increased by high-frequency stimulation of the BLA or BMA (25, 31). In other words, BLA or BMA stimulation had no effect on the saturated LTP, suggesting that BLA or BMA neurons modulate the mechanism involved in tetanus-induced LTP. For example, BLA or BMA neurons may play a role in lowering the threshold of LTP induction.

Whether the influences of the BLA and BMA on hippocampal plasticity are independent of each other was also investigated. In BLA-lesioned rats, the magnitude of dentate gyrus LTP was significantly reduced, but a small LTP still remained. Similarly, residual LTP was observed in BMA-lesioned rats (25). The magnitude of dentate gyrus LTP in rats that received both BLA and BMA lesions was almost the same as that in BLA- or BMA-lesioned rats (25). However, facilitation of dentate gyrus LTP by electrical stimulation of BMA was observed in BLA-lesioned rats and vice versa, suggesting that the BLA and BMA have independent neural outputs to the dentate gyrus and facilitate the induction of LTP (25). The roles of the BLA and BMA can be explained by the following model. There may be two different types of dentate gyrus LTP, i.e., amygdala-dependent and -independent LTP. At the amygdala-dependent synapses, spontaneous BLA and BMA neuron activities play a role in facilitating the induction of LTP in association with activation of the perforant path. At the amygdala-independent synapses, LTP is established only by activation of the perforant path. If the BLA or BMA is lesioned, spontaneous activity of BMA or BLA neurons alone is not sufficient to facilitate LTP, resulting in no LTP at the amygdala-dependent synapses. When BMA or BLA neurons are sufficiently activated by electrical stimulation, amygdala-dependent LTP is induced even if either the BLA or BMA is destroyed.

Our findings are confirmed by the findings of other laboratories. Jas et al. (32) have reported that early LTP in the dentate gyrus was reinforced into late LTP by stimulation of the BLA of rats and that the effect of BLA stimulation disappeared after transection of the fimbria-fornix, suggesting that septo-hippocampal fornical projection is important for LTP maintenance. Akirav and Richter-Levin (33) have reported that a priming stimulation to the BLA prior to application of tetanic stimulation to the perforant path resulted in enhancement of LTP in the dentate gyrus. Akirav and Richter-Levin (34) have also reported that behavioral stress induced 1 h before tetanic stimulation to the perforant path inhibited the induction of LTP in the dentate gyrus and that the behavioral stress blocked the enhancement of dentate gyrus LTP by BLA stimulation. The opposite effects of behavioral stress and direct electrical stimulation of the BLA on dentate gyrus LTP seem to be inconsistent with the hypothesis that the BLA mediates emotional responses to behavioral stress. Akirav and Richter-Levin (34) have proposed that the activation of the BLA, either by behavioral stress or by direct electrical stimulation, has a biphasic effect on hippocampal plasticity: an immediate excitatory effect and a longer-lasting inhibitory effect.

6. Induction of hippocampal LTP by MeA

The role of MeA is unique. Single-pulse electrical stimulation of the MeA did not evoke any apparent field potentials in the dentate gyrus, but when applied simultaneously with or 10 – 100 ms prior to perforant path stimulation, significantly enhanced the dentate gyrus field potentials
evoked by perforant path stimulation (35). More interestingly, when high-frequency stimulation (100 Hz for 1 s) was applied to the MeA, the dentate gyrus population spikes evoked by perforant path stimulation was increased, and the potentiation lasted for more than 60 min (35). It should be noted that facilitation of dentate gyrus LTP by the BLA and BMA requires simultaneous activation of the perforant path, while the MeA-induced potentiation does not require activation of the perforant path. In other words, modulation by the BLA and BMA is homosynaptic, while modulation by the MeA is heterosynaptic. The MeA-induced long-lasting potentiation was observed for the population spike, but not for the excitatory postsynaptic potential (36), indicating the potentiation does not reflect changes in synaptic functions. The dissociation between the degree of potentiation in the population spike and excitatory postsynaptic potential may be caused by 1) a change in the internal firing capacity of the postsynaptic cells or 2) a change in the balance between the excitatory and inhibitory inputs activated by stimulation of the afferents. The MeA-induced spike potentiation is probably caused by a change in the internal firing characteristics of the dentate granule cells, because it was not affected by blocking γ-aminobutyrate (GABA) mediated inhibition with the GABA blocker picrotoxin (36). Furthermore, the activation of NMDA receptors is essentially required for the induction of MeA-induced spike potentiation in the dentate gyrus, and subcortical afferents contribute to the establishment of potentiation (37).

The MeA sends a projection of vasopressin-containing fibers to the hippocampus in the rat (38). Electrical stimulation of the MeA (5 – 15 V, 0.5-ms pulse duration, 10 pulses at 100 Hz) produced a depression in the amplitude of population spike at the CA1 region of the hippocampus of anesthetized rats, and the effect was blocked by a vasopressin receptor antagonist, suggesting that vasopressin fibers play a role in suppressing neuron excitability in CA1 of the hippocampus (39). However, it is unknown whether vasopressin is involved in MeA-induced spike potentiation in the dentate gyrus.

7. Conclusions

Table 1 summarizes influences of inactivation or activation of amygdaloid nuclei on LTP at the perforant path-dentate gyrus granule cell synapses of anesthetized rats. Although studies to date clearly demonstrate that the formation of LTP in the dentate gyrus is modulated by neural inputs from BLA, BMA or MeA, several questions remain to be unsolved: 1) detailed neural projection pathway from each amygdaloid nucleus to the hippocampus, 2) neurotransmitter(s) involved in modulation of hippocampal LTP, 3) whether or not the amygdala modulates LTP in other hippocampal regions than the dentate gyrus, 4) whether or not hippocampal LTP is affected by emotional stimuli thought to involve the amygdala and 5) molecular mechanisms. It would also be interesting to know the roles of other brain regions in the emotion system, including the hypothalamus (40). Further investigations on modulation of hippocampal LTP by the amygdala will help to elucidate cellular mechanisms underlying memory enhancement associated with emotions and may give clues for the development of novel memory-enhancing drugs.

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