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Frequency-dependent associative long-term potentiation at the hippocampal mossy fiber–CA3 synapse

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ABSTRACT **The mossy fiber–CA3 synapse displays an *N*-methyl-D-aspartate-receptor-independent μ-opioid-receptor-dependent form of long-term potentiation (LTP) that is thought not to display cooperativity or associativity with coactive afferents. However, because mossy fiber LTP requires repetitive synaptic activity for its induction, we reevaluated cooperativity and associativity at this synapse by using trains of mossy fiber stimulation. Moderate-, but not low-, intensity trains induced mossy fiber LTP, indicating cooperativity. Low-intensity mossy fiber trains that were normally ineffective in inducing LTP could induce mossy fiber LTP when delivered in conjunction with trains delivered to commissural–CA3 afferents. Associative mossy fiber LTP also could be induced with single mossy fiber pulses when delivered with commissural trains in the presence of a μ-opioid-receptor agonist. Our findings suggest a frequency-dependent variation of Hebbian associative LTP induction that is regulated by the release of endogenous opioid peptides.**

Hippocampal long-term potentiation (LTP) is a relatively long-lasting change in synaptic strength that remains a favored model of the cellular processes that may underlie information storage in the vertebrate brain (1, 2). Two important and closely related features of LTP induction are that a threshold level of afferent coactivity is essential for the induction of LTP (cooperativity) (3) and that LTP can be induced at synapses that are active simultaneously with the intense activity of other afferents (associativity) (4, 5). These features, derived principally from the dependence of LTP induction on postsynaptic *N*-methyl-D-aspartate (NMDA) glutamate receptors (2), are thought to reflect an associative mechanism of information storage in a manner postulated by Hebb (6).

The hippocampal mossy fiber–CA3 synapse displays an unusual NMDA-receptor-independent (7–9) form of LTP that is reportedly insensitive to the intensity of high-frequency stimulation (9, 10) and is not induced by single pulses delivered in conjunction with either postsynaptic depolarization (8, 9) or coactive afferents (9, 11), findings that suggest an absence of Hebbian cooperative and associative processes at this synapse (9–11). These findings led some investigators to suggest that mossy fiber LTP is a nonassociative form of hippocampal synaptic plasticity that utilizes mechanisms of induction that are independent of postsynaptic depolarization and that it may utilize exclusively presynaptic mechanisms of induction (9–10).

An alternative view is that the inability of mossy fiber responses to display associative LTP arises from its unique requirements for LTP induction. Repetitive mossy fiber activity is required for induction of mossy fiber LTP (8–10, 12). Thus the inability of single mossy fiber pulses to display associativity could reflect an absence of factors associated with high-frequency mossy fiber activity, rather than an independence of LTP induction from postsynaptic processes (8). The release of opioid peptides by the mossy fibers may be one such frequency-dependent factor (12–17). Proenkephalin- and prodynorphin-derived opioid peptides are released by mossy fiber terminals in a frequency-dependent manner (18–20), and activation of μ opioid receptors is essential for the induction of nondecremental mossy fiber LTP in rat hippocampus (refs. 12 and 15, but see ref. 21). Furthermore, although sustained trains are necessary to induce mossy fiber LTP, brief trains can induce mossy fiber LTP when delivered in the presence of a μ-opioid-receptor agonist (12). Here we demonstrate that repetitive mossy fiber stimulation permits cooperative and associative LTP at mossy fiber synapses and that the frequency-dependent activation of μ opioid receptors underlies this effect. Our findings suggest that the mossy fiber synapse utilizes a frequency-dependent peptidergic cellular mechanism for the induction of associative LTP, which appears to confer activity-dependent constraints on its induction.

METHODS

Seventy-five adult male Sprague–Dawley rats were anesthetized with sodium pentobarbital (60 mg/kg), the head was mounted in a stereotaxic frame, and electrodes were placed using stereotaxic coordinates. CA3 responses were collected as described (12, 15). Briefly, mossy fiber responses were evoked by stimulation of the mossy fiber bundle in area CA3b/c, and commissural responses were evoked by stimulating the contralateral CA3 region homotopic to the recording electrode. Responses were recorded in each animal by a single Teflon-coated stainless steel electrode placed in the stratum lucidum of area CA3a. Low-frequency responses were evoked at 0.033 Hz using a current intensity (10–300 μA) that elicited responses that were either 25% (mossy fiber) or 50% (commissural) of the maximal peak amplitude. Responses were amplified, filtered at 0.1 Hz to 1 kHz, digitized (10,000 Hz) using a 33-MHz 80486 microcomputer, and then stored for off-line analysis. Measurement of the magnitude of both mossy fiber– and commissural–CA3 responses was confined to the initial slope of field excitatory postsynaptic potential (EPSP) measured between 2 and 3 msec after response onset. The electroencephalogram was monitored for at least 1 min after delivery of trains, and no animals displayed afterdischarges after tetanization. LTP magnitude was measured between 26 and 30 min after delivery of trains. Paired pulse facilitation was measured at this time period using a 50-msec interpulse interval, with pulses delivered at

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Abbreviations: LTP, long-term potentiation; EPSP, excitatory postsynaptic potential; DAMGO, [D-Ala^2,*N*-Me-Phe^4,Gly-ol^5]enkephalin; (±)-CPP, (±)-3,2-carboxypiperazin-4-propyl-1-phosphonic acid; CTOP, D-Phe-Cys-Tyr-D-Trp-Orn-Pen-Thr-NH_2, where Orn is ornithine and Pen is penicillamine; NMDA, *N*-methyl-D-aspartate.

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the intensity used to evoke single responses. Treatment effects were evaluated using an ANOVA.

The μ-receptor-selective agonist [D-Ala^2,N-Me-Phe^4,Gly-ol^5]enkephalin (DAMGO; 100 pmol; Research Biochemicals International) and the μ-receptor-selective antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Pen-Thr-NH_2, where Orn is ornithine and Pen is penicillamine; (CTOP; ref. 22; 3 nmol; Peninsula Laboratories) were delivered locally to area CA3 via pressure ejection (12). The NMDA antagonist (±)-3,2-carboxypiperazine-4-propyl-1-phosphonic acid [(±)-CPP, RBI] was dissolved in saline and administered intraperitoneally (10 mg/kg) at least 90 min prior to delivery of high-frequency trains.

Verification of mossy fiber responses was based on both stereotaxic coordinates and electrophysiological criteria as described (12), including the evocation of an antidromic response in the dentate gyrus, and temporal correspondence of the antidromically elicited spike with the orthodromically elicited presynaptic volley. In addition, electrode placements were verified periodically by histological techniques in 10% of the subject population.

RESULTS

Essential for a convincing demonstration of an absence of cooperativity is a demonstration that stimulation parameters that are sufficient to induce LTP at moderate intensities also can induce LTP even at very low intensities. In the present study, we used trains of mossy fiber stimuli (50 pulses at 100 Hz) that reliably induce LTP at moderate stimulation intensities (12). Trains delivered to the mossy fibers at 25% of maximum intensity failed to induce mossy fiber LTP (mean percent change in mossy fiber field EPSP slopes after tetanization = −1.6 ± 9%). In contrast, trains delivered at 50% of the maximum intensity potentiated mossy fiber field EPSP slopes [mean percent increase = +50 ± 13%; $F(1,7) = 10.3$; $P < 0.01$]. Mossy fiber LTP developed maximal amplitude slowly over the course of 1 h and displayed a concomitant decrease in paired pulse facilitation [mean percent facilitation of baseline EPSPs = +65 ± 13% and as measured after tetanization = +26 ± 12%; $F(1,3) = 10.2$; $P < 0.05$, $n = 4$], effects that are characteristic of mossy fiber LTP (12, 15–17, 23, 24).

The foregoing results indicate that a threshold level of intensity must be provided to induce mossy fiber LTP. We tested whether stimulation of separate afferents to CA3 pyramidal cells could substitute for intense mossy fiber stimulation. High-frequency stimulation (100 Hz for 1 sec at 50% intensity) of commissural–CA3 afferents potentiated commissural but not mossy fiber responses (mean percent increase in commissural response slopes measured between 11 and 15 min after tetanus = +87 ± 22%; mean increase in mossy fiber responses = −2 ±2%; $n = 5$; Fig. 1*A*), demonstrating independence of the two pathways. Delivery of trains to the mossy fibers using parameters found above to be ineffective for inducing LTP (50 pulses at 100 Hz at 25% of maximal current intensity) simultaneously with commissural stimulation (50 pulses at 100 Hz at 50% of maximal current intensity) resulted in potentiation of mossy fiber responses (Fig. 1). This potentiation was significant compared to changes in mossy fiber responses produced by identical mossy fiber trains delivered 600 msec out of phase with the commissural trains (mean increase in mossy fiber responses produced by paired stimulation = +36 ± 5% and by unpaired stimulation = −7 ± 4%; $n = 5$ per condition; Fig. 2*A*).

Potentiation of mossy fiber responses produced by coactivation of commissural afferents displayed a magnitude comparable to that of homosynaptically induced mossy fiber LTP [+36 ± 5% increase for associative potentiation vs. +39 ± 10% increase after 50 pulses at 50% intensity; $F(1,12) = 0.06$; $P > 0.05$; $n = 14$], developed maximal amplitude slowly,

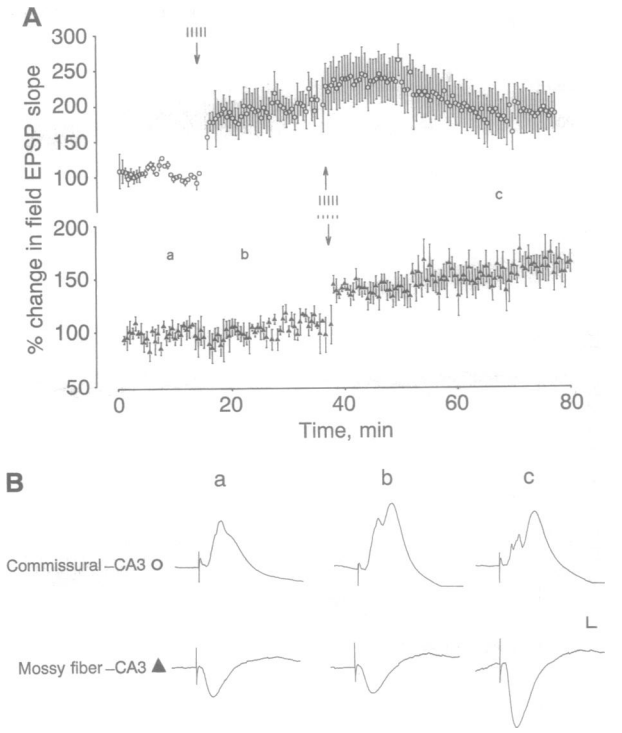

FIG. 1. Associative mossy fiber–CA3 LTP is induced by coactivation of commissural–CA3 afferents. Each plot represents the percent change in amplitude (mean ± SEM) for five subjects. (*A*) Associative mossy fiber LTP induced by trains of mossy fiber stimulation. In each animal, mossy fiber responses (▲) were evoked at current intensities evoking a response that was 25% of maximal amplitude, and commissural–CA3 responses (○) were evoked using current intensities evoking responses that were 50% of the maximal amplitude. A single train delivered to commissural–CA3 afferents (50 pulses at 100 Hz, first arrow from the left) potentiated only in commissural–CA3 field EPSP slopes. Delivery of a similar commissural train simultaneously with a 50-pulse mossy fiber train at 25% intensity (second arrow from the left) resulted in a potentiation of mossy fiber field EPSPs ($n = 5$). (*B*) Representative mossy fiber–CA3 and commissural–CA3 waveforms recorded during baseline (traces a), after a tetanus to commissural afferents (traces b), and after stimulation of mossy fiber and commissural afferents (traces c). (Calibration: 0.25 mV and 5 msec.)

characteristic of the development of mossy fiber LTP *in vivo* (12, 15, 16, 23), and produced a reduction in the magnitude of mossy fiber paired-pulse facilitation [mean percent facilitation of baseline EPSPs = +46 ± 12%, as measured after tetanization = +22 ± 11%; $F(1,3) = 61.9$; $P < 0.01$; $n = 4$]. The induction of associative mossy fiber LTP also occluded subsequent mossy fiber LTP [mean increase with associative mossy fiber LTP = +36 ± 5%; mean additional increase after a 50-pulse train delivered 50–60 min later at 50% intensity = −9 ± 15%; $F(1,8) = 52.8$; $P < 0.001$; $n = 4$]. Further, as we reported (12, 15) for homosynaptic mossy fiber LTP, associative mossy fiber potentiation is blocked by 3 nmol of the μ-opioid-receptor-selective antagonist CTOP (mean percent change in mossy fiber responses = +36 ± 5%, $n = 5$; in the presence of 3 nmol of CTOP = −1.2 ± 5%, $n = 5$), while potentiation of commissural–CA3 responses is unaffected by this drug (Fig. 2*B*).

We also addressed the possible processes by which commissural afferents contribute to associative mossy fiber LTP induction by administering the competitive NMDA receptor antagonist (±)-CPP (10 mg/kg i.p.). (±)-CPP administered 90 min prior to tetanization blocked LTP induction in commissural afferents, whereas this treatment had no effect on mossy fiber LTP induced homosynaptically (Fig. 3*A*), as

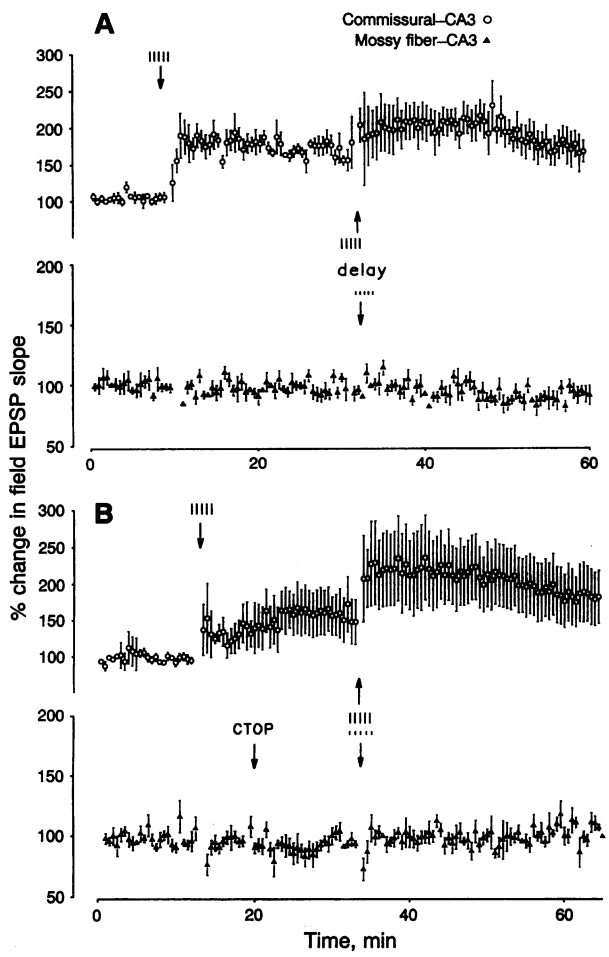

FIG. 2. Induction of associative mossy fiber LTP requires temporal contiguity of trains and μ-opioid-receptor activation. Each plot represents the percent change in amplitude (mean ± SEM) for four or five subjects. (*A*) As in Fig. 1, except that the mossy fiber train was delivered 600 msec after the commissural train ($n = 5$). Associative mossy fiber LTP was not observed with unpaired trains [$F(1,8) = 52.8$; $P < 0.001$, as compared with mossy fiber potentiation induced by paired trains in Fig. 3], indicating that associative mossy fiber LTP requires temporal contiguity of trains. (*B*) Application of 3 nmol of CTOP to the CA3 region 10 min prior to delivery of paired trains did not alter mossy fiber responses (▲) but blocked the induction of associative mossy fiber LTP [$F(1,8) = 30.7$; $n = 5$; $P < 0.001$, as compared with potentiation induced by paired trains in Fig. 1]. CTOP did not alter significantly the magnitude of commissural–CA3 LTP (○) induced by the second train [mean percent increase of commissural responses in control animals after delivery of a second train = +28 ± 7%; mean percent increase produced by a second train in the presence of CTOP = +30 ± 12%; $F(1,7) = 0.02$; $P > 0.05$; $n = 9$].

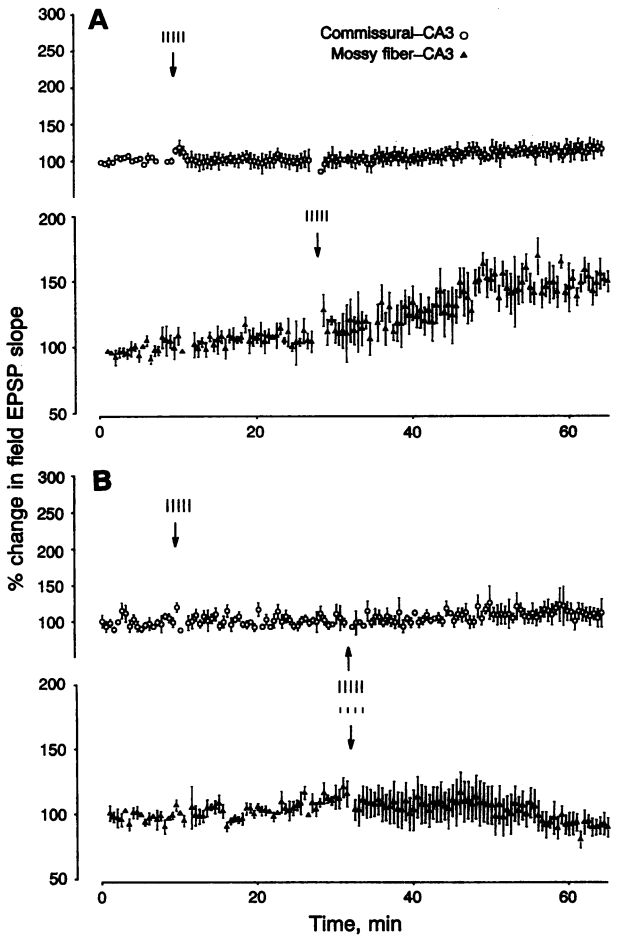

FIG. 3. Induction of associative mossy fiber LTP, but not homosynaptically induced mossy fiber LTP, is blocked by the NMDA-receptor antagonist (±)-CPP. Each plot represents the percent change in amplitude (mean ± SEM) for four or five subjects. (*A*) Systemic administration of the competitive NMDA-receptor antagonist (±)-CPP (10 mg/kg) 90 min prior to delivery of a 50-pulse 100-Hz train (50% of maximal intensity) blocked potentiation of commissural–CA3 responses (○), whereas, in the same animals, potentiation of mossy fiber responses (▲) induced with a 50-pulse 100-Hz train (50% of maximal intensity) was not altered by (±)-CPP ($n = 4$). (*B*) (±)-CPP administered 90 min prior to tetanization blocked LTP induction in commissural responses. (±)-CPP also blocked potentiation of mossy fiber responses induced by commissural trains (50-pulse 100-Hz train, 50% of maximal intensity) paired with mossy fiber trains (50 pulses at 100 Hz) delivered at 25% of the maximal current intensity [$F(1,8) = 17.52$; $P < 0.01$, as compared with data presented in Fig. 1; $n = 5$].

reported (7–9, 12). However, this drug blocked mossy fiber LTP induced associatively by pairing low-intensity mossy fiber trains with commissural trains (Fig. 3*B*).

The activation of μ opioid receptors is one factor underlying the requirement of repetitive mossy fiber activity for the induction of mossy fiber LTP (12). We therefore determined whether μ-opioid-receptor activation also underlies the frequency dependence of associative mossy fiber LTP by using a single-pulse associativity paradigm (11). As reported (11), single mossy fiber pulses (50% intensity) paired with brief commissural trains (50-msec 100-Hz trains delivered at 5 Hz for five 2-sec periods at 50% of the maximal current intensity) did not induce associative mossy fiber LTP (mean percent change in mossy fiber field EPSP slopes stimulated in the presence of lactated Ringer's vehicle = −4 ± 4%, $n = 5$; Fig. 4*A*). We then assessed single-pulse associativity in the presence of a μ-opioid-receptor agonist. As we reported (12), application of 100 pmol of the selective μ-opioid-receptor agonist DAMGO did not alter mossy fiber field EPSP slopes (Fig. 4*B*). However, when single mossy fiber pulses were delivered in conjunction with commissural stimulation in the presence of 100 pmol of DAMGO, mossy fiber LTP was observed (mean percent increase after stimulation in the presence of DAMGO = +28 ± 2%, $n = 4$; Fig. 4*B*). Mossy fiber LTP induced with single pulses reduced the magnitude of paired pulse facilitation [+40 ± 7% as measured at baseline vs. +21 ± 2% after stimulation; $F(1,3) = 11.23$; $P < 0.05$; $n = 4$]. In contrast, potentiation of mossy fiber responses was not observed after either mossy fiber stimulation by itself (5-Hz 2-sec trains delivered at 50% intensity five times), delivered in the presence of 100 pmol of DAMGO (mean percent increase = −2 ± 7%, $n = 5$; Fig. 4*C*), or stimulation of commissural afferents (50-msec 100-Hz trains delivered at 5 Hz for five 2-sec periods) in the presence of 100 pmol of

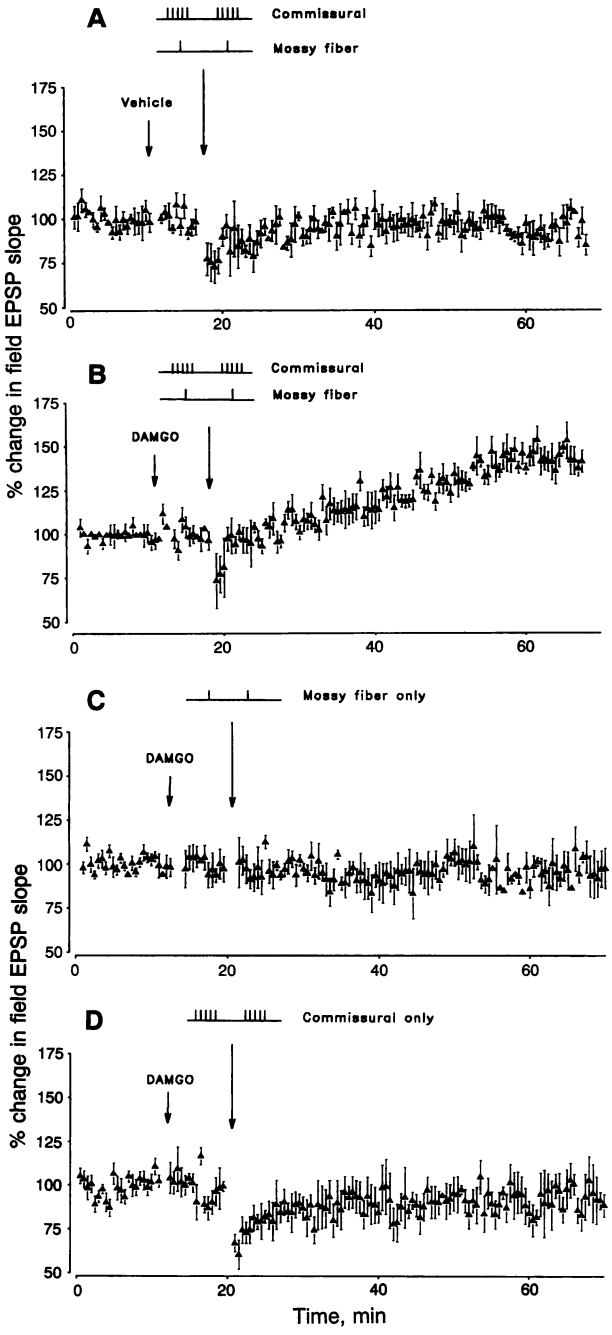

FIG. 4. Associative mossy fiber LTP is induced by pairing single mossy fiber pulses with commissural trains in the presence of a μ-opioid-receptor agonist. Each plot represents the percent change in amplitude (mean ± SEM) for four or five subjects. (*A*) Trains delivered to commissural–CA3 afferents (100-Hz 50-msec trains, delivered every 200 msec for five 2-sec periods) in conjunction with single mossy fiber pulses delivered at 50% of the maximal current intensity and in the presence of lactated Ringer's vehicle did not induce mossy fiber LTP ($n = 5$). (*B*) In contrast, these same stimulation parameters, when delivered in the presence of 100 pmol of DAMGO, produced significant potentiated mossy fiber responses [$F(1,7) = 48.5$; $P < 0.001$, as compared with data from *A*; $n = 4$). (*C*) Single mossy fiber pulses delivered in the presence of 100 pmol of DAMGO (five 5-Hz 2-sec trains) but without coactivation of commissural afferents did not potentiate mossy fiber responses [$F(1,7) = 15.1$; $P < 0.001$, as compared with *B*; $n = 5$). (*D*) Commissural trains (100-Hz 50-msec trains, delivered every 200 msec for five 2-sec periods) delivered in the presence of 100 pmol of DAMGO (five 5-Hz 2-sec trains) but without single mossy fiber pulses did not potentiate mossy fiber responses [$F(1,6) = 6.74$; $P < 0.05$, as compared with *B*; $n = 4$).

DAMGO (mean percent increase = −20 ± 18%, $n = 4$; Fig. 4*D*). Often these conditions produced a depression of mossy fiber responses (Fig. 4 *A*, *C*, and *D*).

DISCUSSION

At synapses lacking cooperativity, it would be expected that trains sufficient to induce LTP at moderate intensities would induce LTP even at very low current intensities. However, our results indicate that mossy-fiber LTP is not produced by sustained high-frequency stimulation of a limited number of fibers. It is therefore unlikely that single mossy fibers are capable of generating LTP, contradicting the suggestion that mossy fibers utilize an intensity-independent and exclusively presynaptic mechanism of LTP induction (9, 10, 21). Rather, it appears that processes provided by intense stimulation and, therefore, the activity of a sufficient number of mossy fiber afferents are necessary for induction of LTP at this synapse.

Our results also indicate that high-frequency stimulation of the nonopioidergic commissural afferent system in conjunction with low-intensity mossy fiber trains can potentiate mossy fiber responses. This potentiation is blocked by a μ-opioid-receptor antagonist, occludes the induction of homosynaptic mossy fiber LTP, and displays a time course (12, 15, 16, 23) and changes in paired pulse facilitation (9, 24) that are observed with homosynaptic mossy fiber LTP, suggesting that coactivation of mossy fiber synapses with commissural–CA3 afferents induced mossy fiber LTP. Additionally, mossy fiber trains delivered out-of-phase with commissural trains failed to induce mossy fiber LTP, suggesting a temporally restricted window during which coactive afferents can contribute to mossy fiber LTP induction, as is observed with associative LTP at other hippocampal synapses (4, 5).

Although repetitive mossy fiber stimulation is necessary to induce associative mossy fiber LTP, exogenous application of a μ-opioid-receptor agonist permits the induction of associative mossy fiber LTP by single mossy fiber responses paired with trains of commissural stimulation. This suggests that the activation of μ opioid receptors by the frequency-dependent release of endogenous opioid peptides is one condition underlying the frequency dependence of associative mossy fiber LTP induction. Additionally, low-frequency mossy fiber stimulation delivered in the presence of a μ-opioid-receptor agonist induced mossy fiber LTP only when paired with tetanization of commissural afferents. This suggests that the activation of μ opioid receptors and the coactivation of a sufficient number of afferents are distinct conditions that are both necessary for the induction of mossy fiber LTP. Furthermore, tetanization of commissural afferents in the presence of DAMGO does not potentiate mossy fiber responses, indicating that CA3 pyramidal cell activity and μ-opioid-receptor activation are insufficient to induce mossy fiber LTP. This suggests that presynaptic mossy fiber activity is essential for the associative induction of mossy fiber LTP. Thus, these findings suggest that μ-opioid-receptor activation, intense afferent coactivation, and presynaptic mossy fiber activity are each conditions that are necessary for the induction of mossy fiber LTP.

Essential for the occurrence of Hebbian associative processes is a postsynaptic convergence of contributing factors (6). The demonstration of cooperative and associative processes at the mossy fiber synapse does not, however, indicate the involvement of postsynaptic processes in the induction of mossy fiber LTP, for interactions among coactive presynaptic terminals could underlie this phenomena (3). However, we report here that mossy fiber LTP induced in an associative manner is attenuated by the NMDA receptor antagonist (±)-CPP. Because mossy fiber LTP induced by homosynaptic mossy fiber stimulation is not altered by (±)-CPP, it is likely that coactive commissural afferents can contribute to

mossy fiber LTP induction via processes that are provided by NMDA-receptor activation. Thus, it is likely that some common processes of LTP induction are utilized by both of these forms of LTP. Furthermore, because NMDA-receptor antagonists are thought to block LTP induction by blocking postsynaptic NMDA receptors (2, 25, 26), the processes by which coactive commissural afferents contribute to mossy fiber LTP induction likely are localized to the postsynaptic element. These data and the present and previous (10) findings indicating that mossy fiber LTP is specific to tetanized synapses suggest that Hebbian associative processes operate at the mossy fiber synapse (8, 27).

The induction of LTP at the mossy fiber–CA3 synapse *in vivo* appears to obey Hebbian rules requiring temporal contiguity of pre- and postsynaptic factors. However, it differs from most hippocampal synapses with regard to the kind of presynaptic activity that is required in that the induction of both associative and homosynaptic mossy fiber LTP requires repetitive presynaptic activity. This additional requirement may be thought of as a variation of Hebbian rules governing the induction of hippocampal synaptic plasticity and may reflect additional constraints imposed on the mossy fiber synapse that serve to limit the conditions during which mossy fiber LTP can be induced. For instance, additional constraints may be imposed on synaptic populations that have a relatively strong influence on hippocampal function. It therefore is of interest that some models of distributed information storage within the hippocampus propose that mossy fiber synapses serve as "detonator" synapses that influence greatly the induction of plasticity in other synaptic populations (28–30). Alternatively, constraints that tightly regulate the induction of LTP also may be associated with synapses that exhibit extensive modifications in response to LTP induction. It therefore may be of relevance that mossy fiber LTP is likely associated with subsequent mossy fiber synaptogenesis (31, 32).

Because the induction of both homosynaptic (12) and associative mossy fiber LTP requires repetitive presynaptic activity, it would be expected that, in the intact animal, the induction of mossy fiber LTP also would require repetitive presynaptic granule cell activity. However, repetitive dentate granule cell activity is suggested to occur only rarely in the behaving animal (33, 34), although repetitive granule cell firing may occur during hippocampal θ rhythm (35, 36). Thus if mossy fiber LTP occurs normally in behaving animals, then its induction may be limited to periods of hippocampal θ rhythm, such as occurs during exploratory behaviors (37).

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