Long-Term Depression of Temporoammonic-CA1 Hippocampal Synaptic Transmission

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Dvorak-Carbone, Hannah and Erin M. Schuman. Long-term depression of temporoammonic-CA1 hippocampal synaptic transmission. J. Neurophysiol. 81: 1036–1044, 1999. The temporoammonic pathway, the direct projection from layer III of the entorhinal cortex to area CA1 of the hippocampus, includes both excitatory and inhibitory components that are positioned to be an important source of modulation of the hippocampal output. However, little is known about synaptic plasticity in this pathway. We used field recordings in hippocampal slices prepared from mature (6- to 8-wk old) rats to study long-term depression (LTD) in the temporoammonic pathway. Low-frequency (1 Hz) stimulation (LFS) for 10 min resulted in a depression of the field response that lasted for ≥1 h. This depression was saturable by multiple applications of LFS. LTD induction was unaffected by the blockade of either fast (GABAA) or slow (GABAB) inhibition. Temporoammonic LTD was inhibited by the presence of the N-methyl-D-aspartate (NMDA) receptor antagonist AP5, suggesting a dependence on calcium influx. Full recovery from depression could be induced by high-frequency (100 Hz) stimulation (HFS); in vivo, LTP of the temporoammonic pathway, whose activity can modulate plasticity in the hippocampus, is referred to as the temporoammonic pathway (Maccaferri and McBain 1995; Ramón y Cajal 1911) because of its origins in the entorhinal cortex (in the temporal lobe) and its termination in CA1, part of the cornu ammonis of the hippocampus. Unlike the perforant path, which consists of axons from stellate excitatory neurons of layer II of the entorhinal cortex, the temporoammonic pathway consists of axons from pyramidal cells of layer III of the entorhinal cortex (Steward and Scoville 1976). These temporoammonic axons terminate preferentially in the area of the distal dendrites of the pyramidal cells, stratum lacunosum-moleculare (SLM). These axons make asymmetric (and hence probably excitatory) synapses, >90% of which are onto the spines of CA1 pyramidal cells (Desmond et al. 1994). Temporoammonic axons also synapse onto the inhibitory basket and chandelier cells of CA1 (Kiss et al. 1996) and are likely to innervate the interneurons of SLM (Lacaille and Schwartz-kroin 1988; Vida et al. 1998).

There is some controversy as to whether the temporoammonic input to the hippocampus is primarily excitatory or primarily inhibitory (see Soltész and Jones 1995). Field recordings in vitro (Colbert and Levy 1992; Doller and Weight 1982) and in vivo (Leung et al. 1995; Yeckel and Berger 1990, 1995) reveal a population excitatory postsynaptic potential (EPSP) in SLM after stimulation of the temporoammonic pathway, supporting the ultrastructural evidence for an excitatory input onto the distal dendrites of CA1 neurons. However, intracellular recordings (Empson and Heinemann 1995) show a mixed response, including a monosynaptic glutamatergic EPSP and a disynaptic inhibitory postsynaptic potential with both GABA_A and GABA_B components.

Various forms of short- and long-term plasticity have been extensively studied at all three synapses in the trisynaptic circuit of the hippocampus (Bliss and Collingridge 1993). As yet, however, relatively little is known about plasticity in the temporoammonic pathway, whose activity can modulate plasticity in the Schaffer collateral pathway to CA1 (Levy et al. 1998) and whose position in the hippocampal circuitry suggests a potent role in the modulation of hippocampal output from CA1. A previous study reported induction of long-term potentiation (LTP) in this pathway in vitro only when fast inhibition was blocked by addition of the GABA_A antagonist bicuculline (Colbert and Levy 1993); in vivo, LTP of the excitatory current sink in the distal dendrites of area CA1 evoked by stimulation of the perforant path (including tem-
poroammonic axons) was reported after tetanic stimulation (Leung et al. 1995). In this study we report that long-term depression (LTD) can readily be induced in the temporoammonic pathway, in slices prepared from mature rats, by means of low-frequency stimulation (LFS). Some of these results previously appeared in abstract form (Dvorak and Schuman 1996).

**METHODS**

**Tissue preparation**

Slices were prepared from 6- to 8-wk old male Sprague-Dawley rats. All use of animals was performed according to the guidelines of the Caltech Institutional Animal Care and Use Committee. Rats were decapitated after halothane anesthesia, and the brain was rapidly removed to ice-cold, oxygenated artificial cerebrospinal fluid (ACSF) containing (in mM) 119 NaCl, 2.5 KCl, 1.3 MgSO4, 2.4 CaCl2, 1.0 NaH2PO4, 26.2 NaHCO3, and 11.0 glucose. The dorsal surface of the posterior half of each hemisphere was glued onto the stage of a cooled tissue slicer (OTS-3000 – 04; FHC) and covered with a warmed chamber at room temperature for 1 h before experiments were started. Further microdissection was performed either in ice-cold ACSF immediately after slice preparation or in the recording chamber before the start of the experiment. All electrophysiology was done with the slices submerged and constantly perfused with oxygenated ACSF at room temperature.

To clearly isolate the temporoammonic response, it was necessary to further dissect the slice (see Fig. 1). The entire dentate gyrus was removed to eliminate the possibility of activation of the trisynaptic pathway and to prevent contamination of a field response recorded in SLM by the much larger field elicited in dentate gyrus by concurrent activation of the perforant path. In most experiments, including all those in which bicuculline was used, CA3 was also removed to prevent induction of seizure-like activity as well as to eliminate the possibility of disynaptic activation via the perforant path projection to CA3. Also, a cut was made through stratum radiatum (SR) in distal CA1 (near the subiculum) perpendicular to the cell body layer to prevent antidromic activation of Schaffer collaterals by the stimulating electrode in SLM (see Fig. 1). Schaffer collaterals do not enter SLM to any appreciable extent (Amaral and Witter 1989), so this cut cleanly isolates temporoammonic axons.

**Electrophysiology**

Bipolar tungsten electrodes, either concentric or paired needles, were used for stimulation. One electrode was placed in SR to stimulate the Schaffer collaterals; the other was placed in SLM to stimulate the temporoammonic pathway (Fig. 1). Stimulus pulses were 100 μs long, monophasic, and ranged from 10 to 100 μA in the Schaffer collateral pathway and 100 to 200 μA in the temporoammonic pathway. Stimulus intensities were selected to produce submaximal responses with no population spike. Field recordings were made with low-resistance micropipettes filled with 3 M NaCl. The Schaffer collateral response was recorded in SR, and the temporoammonic response was recorded in SLM. Separation of the two pathways was further confirmed by the observation of a positive-going field potential in the other layer (Fig. 1) (Colbert and Levy 1992).

The following stimulation paradigms were used: high-frequency stimulation (HFS) = 100 Hz for 1 s, repeated four times at 20- or 30-s intervals; θ-burst stimulation (TBS) = four bursts of five pulses at 100 Hz, 200 ms between bursts, repeated four times at 20- or 30-s intervals; LFS = 1 Hz stimulation for 10 min. All stimulus pulses were of the same length and amplitude as test pulses. Test pulses were applied once every 20 or 30 s to each pathway. The initial slope of the field potential after the end of the fiber volley was measured.

Drugs were applied by dilution of concentrated stock solutions into the perfusion medium. Stock solutions were made up in water, with the exception of nifedipine, which was prepared in DMSO (×1,000) and stored protected from light. Experiments with nifedipine were performed in low light. CGP 55845A was a kind gift from Novartis (Basel, Switzerland); all other drugs were obtained from Sigma (St. Louis, MO).

**Data analysis**

Data were collected directly onto an IBM-compatible computer with in-house software. All numerical values are listed as means ± SE unless otherwise stated. Depression and potentiation were measured by taking an average of the initial slopes of the field EPSPs (fEPSPs) over 10-min periods immediately after and 20–30 or 50–60 min after the end of LFS, HFS, or TBS. Student’s paired t-test was used to determine statistical significance for
within-group comparisons; the unpaired \( t \)-test was used between groups. Results from each experimental manipulation were compared with the same control group. \( P \) values \( > 0.05 \) are reported in the text as not significant (NS). Points in figures represent means \( \pm \) SE across all experiments; each point is the average of data taken over 5 min. Representative traces, shown in insets, are averages of five consecutive sweeps from a representative experiment, taken 5 min before LFS, HFS, or TBS and 25 min after the end of LFS, HFS, or TBS.

**RESULTS**

**Temporoammonic field response is depressed by LFS**

When LFS (see METHODS) was applied to the temporoammonic pathway in normal ACSF, the response was significantly depressed (Fig. 2A) (mean percent of baseline at 30–40 min, 75.9 \( \pm \) 3.4\%, \( n = 26 \), \( P < 0.0001 \)). This synaptic depression persisted for \( \approx 1 \) h (mean percent of baseline at 60–70 min, 73.7 \( \pm \) 5.0\%, \( n = 7 \), \( P < 0.01 \)) and was not accompanied by any significant changes in the size of the presynaptic fiber volley (Fig. 2A).

During the application of LFS to the temporoammonic pathway, the Schaffer collateral pathway was not stimulated; during the rest of the experiment, test pulses were applied to the Schaffer collateral pathway at the same frequency as to the temporoammonic pathway. Synaptic strength in the Schaffer collateral pathway was not affected, whereas the temporoammonic response was depressed by LFS (Fig. 2A) (mean percent of baseline at 30–40 min, 95.0 \( \pm \) 4.7\%, \( n = 9 \), NS).

LTD has also been observed after LFS of the Schaffer collateral pathway (Mulkey and Malenka 1992) but only in slices prepared from younger animals (Dudek and Bear 1993; Wagner and Alger 1995). When the LFS protocol was applied to the Schaffer collateral pathway in this study, little or no depression was seen. On average, a small but not statistically significant depression of the response was observed (Fig. 2B) (mean percent of baseline at 30–40 min, 87.3 \( \pm \) 6.2\%, \( n = 8 \), NS); this trend was due only to results from two slices that were depressed to 55 and 65\% of baseline.

To determine whether LTD of the temporoammonnic pathway can be saturated, the LFS protocol was applied repeatedly for 10 min every 30 min either four or five times. The response asymptotically approached a level of \( \approx 30–50\% \) of the original baseline (Fig. 2C), reaching its maximally depressed level after three or four epochs of LFS.
GABA-mediated synaptic transmission is not required for temporoammonic LTD

Synaptic depression of the temporoammonic response could be induced in the absence of fast GABAergic inhibition. After the GABA<sub>A</sub> antagonist bicuculline (20 μM) was added to the perfusion solution, a slight but not significant increase in the temporoammonic field response was generally observed (mean percent of original response 20–25 min after bicuculline application, 105 ± 6%, n = 4, NS). The response was allowed to reach a steady baseline for ≥20 min before application of LFS. LFS in the presence of bicuculline induced depression of the field response (Fig. 3) (mean percent of baseline at 30–40 min, 75.7 ± 2.6%, n = 20, P < 0.0001) that was not significantly different from that observed in control slices. This depression lasted ≥1 h (mean percent of baseline at 60–70 min, 79.9 ± 3.2%, n = 14, P < 0.001).

Depression of the temporoammonic response was also possible in the absence of slow, GABA<sub>B</sub>-mediated inhibition. Addition of the GABA<sub>B</sub> antagonist CGP 55845A (1 μM) had no significant effect on the baseline field potential elicited by temporoammonic stimulation (mean percent of original response 20–25 min after CGP 55845A application, 112 ± 7%, n = 5, NS). When LFS was applied in the presence of CGP 55845A, the field response was still significantly depressed (Fig. 3) (mean percent of baseline at 30–40 min, 72.7 ± 3.5%, n = 5, P < 0.01). This amount of depression was also not significantly different from that seen in control slices.

Blockade of NMDA receptor-mediated transmission reduces temporoammonic LTD

What are the early signaling events important for establishing temporoammonic LTD? Calcium ion is an important ini-
was applied again to slices 30 min after washout of the drugs, significant depression was observed (data not shown; mean percent of baseline at 30–40 min, 70.7 ± 4.4%, n = 7, P < 0.0001).

Blockade of muscarinic receptors does not affect temporoammonic LTD

In addition to the temporoammonic projection, SLM of CA1 also receives a substantial cholinergic input from the medial septum (Matthews et al. 1987). Activation of the muscarinic ACh receptor (mAChR) is implicated in other forms of hippocampal synaptic plasticity (Auerbach and Segal 1996). To determine whether mAChRs are involved in temporoammonic LTD, we applied LFS in the presence of 1 μM atropine.

Atropine itself had no significant effect on the temporoammonic field response. In the presence of atropine, the temporoammonic field response was depressed to the same extent as in control ACSF (Fig. 5) (mean percent of baseline at 30–40 min, 75.1 ± 6.5%, n = 4, NS different from control).

Reversal of temporoammonic LTD

To test whether LTD in the temporoammonic pathway is reversible, HFS (see METHODS) was applied either 30 or 60 min after the end of LFS. In experiments conducted in normal ACSF, HFS induced a significant recovery of the depressed synaptic response (Fig. 6A, control), mean percent of original baseline at 20–30 min, 89.4 ± 3.6%, n = 22, P < 0.05). The increase relative to the depressed baseline was 116.3 ± 3.6% of baseline (n = 22, P < 0.001). The reversal of LTD was even greater when HFS was applied in the presence of 20 μM bicuculline (Fig. 6A, bic), mean percent of original baseline at 20–30 min, 115.3 ± 4.8%, n = 18, P < 0.05). The increase relative to the depressed baseline was 150.1 ± 9.1% of baseline (n = 18, P < 0.0001). This difference in response to HFS after LTD is similar to that seen when HFS was applied to naive slices.

Complete reversal of temporoammonic LTD was achieved by repeated application of HFS. In normal ACSF, three applications of HFS at 5-min intervals resulted in a full recovery to the original baseline response, which persisted for 1 h after the last HFS (Fig. 6B) (mean percent of original baseline at 30–40 min after first HFS, 106.8 ± 9.0%, n = 5, significantly different from depressed level of 76.4 ± 4.5% (P < 0.01), NS different from baseline; mean percent of original baseline at 60–70 min, 103.3 ± 6.4%, n = 5, significantly different from depressed level (P < 0.01), NS different from baseline).

Long-term potentiation

In several hippocampal pathways, HFS or TBS can induce long-term potentiation (LTP) (Bliss and Collingridge 1993). When HFS was applied to the temporoammonic pathway in naive slices, little potentiation of the field response was observed (Fig. 7A, control, mean percent of baseline at 20–30 min, 104.0 ± 3.5%, n = 5).

FIG. 5. Temporoammonic LTD does not require activation of muscarinic ACh receptors. LFS applied in the presence of 1 μM atropine (atr) resulted in the same amount of depression as LFS applied in normal ACSF (control, same data as in Fig. 2) or 1 μM atropine (atr). Scale bar: 0.2 mV/30 ms.

FIG. 6. Temporoammonic LTD can be partially or wholly reversed by high-frequency stimulation (HFS = 100 Hz for 1 s). A: in normal ACSF (control, HFS applied to the depressed temporoammonic pathway resulted in a recovery above the depressed baseline but below the original baseline (---)). In the presence of 20 μM bicuculline, HFS resulted in a potentiation significantly above the original baseline. Top: superimposed representative field potentials taken 5 min before and 25 min after HFS of temporoammonic pathway in normal ACSF (control). Bottom: superimposed representative field potentials taken 5 min before and 35 min after the first HFS application. Scale bar: 0.2 mV/30 ms.
107.8 ± 7.5%, n = 7, NS). Furthermore, no potentiation was observed when TBS was applied (Fig. 7B, ○; mean percent of baseline at 20–30 min, 96.3 ± 3.7%, n = 5, NS). For LTP to be induced, a certain level of postsynaptic depolarization must be reached in response to the excitatory input; in some pathways, this requires overcoming the inhibition that is concurrently activated (e.g., see Steward et al. 1990; Wigstrom and Gustafsson 1983). The idea that fast inhibitory transmission opposes the induction of LTP in this pathway was tested by using the GABA<sub>A</sub> antagonist bicuculline. When HFS was applied to the temporoammonic pathway in the presence of 20 μM bicuculline, significant potentiation was observed (Fig. 7A, △) (mean percent of baseline at 20–30 min, 134.2 ± 6.8%, n = 10, P < 0.05). Delivery of TBS in the presence of bicuculline also resulted in significant potentiation (Fig. 7B, △) (mean percent of baseline at 20–30 min, 118.9 ± 7.9%, n = 5, P < 0.05), as was previously observed (Colbert and Levy 1993).

LTP induced by HFS in most hippocampal pathways is dependent on the activation of NMDA receptors (Bliss and Collingridge 1993). We tested whether the potentiation of the temporoammonic pathway seen in the presence of bicuculline required NMDA receptor activation by applying HFS in the presence of both bicuculline (20 μM) and AP5 (50 μM). Under these conditions, HFS did not induce LTP (Fig. 7A, □) (mean percent of baseline at 20–30 min, 104.1 ± 3.3%, n = 4, NS).

**DISCUSSION**

We examined the capacity for long-term synaptic modification of the temporoammonic CA1 synapse in the hippocampus. LTD was consistently induced by simple LFS of the temporoammonic pathway in slices taken from 6- to 8-wk-old animals; the same protocol applied to the Schaffer collateral pathway resulted in little or no depression (Fig. 2B). Other studies reported an age dependence of LTD induction in the Schaffer collateral pathway, with little or no LTD induced by LFS in slices from older animals (Dudek and Bear 1993; Wagner and Alger 1995). Unlike LTD of the Schaffer collateral response, LTD of the temporoammonic response is robust in slices prepared from adult animals. It should be noted, however, that LTD of the commissural input to CA1 has been shown in adult animals in vivo, although only by means of application of a paired-pulse LFS protocol (Thiels et al. 1994).

Repetitive application of LFS to the temporoammonic pathway resulted in saturation of depression at a maximal level of ~40–50% of the original baseline, similar to or lower than that seen in the Schaffer collateral pathway (Dudek and Bear 1993; Mulkey and Malenka 1992). However, after cessation of LFS, the response rebounded somewhat, suggesting that there may be a “floor” below which the temporoammonic response can be pushed only temporarily. This transient, larger depression may also be analogous to the short-term potentiation seen after tetanic stimulation, which then decays away to reveal LTP of lesser magnitude.

LTD in the temporoammonic pathway is independent of GABA<sub>A</sub> or GABA<sub>B</sub> receptor activation. This also contrasts with Schaffer collateral LTD, where LTD induced by LFS in slices from adult animals is enhanced in the presence of the GABA<sub>A</sub> antagonist bicuculline, and LTD in young animals is inhibited by the GABA<sub>B</sub> antagonist CGP 35348 (Wagner and Alger 1995). Although stimulation of the temporoammonic pathway does clearly activate interneurons, which in turn make both GABA<sub>A</sub> and GABA<sub>B</sub>-mediated synapses onto CA1 pyramidal cells (Dvorak and Schuman 1997; Empson and Heinemann 1995), depression of the monosynaptic, excitatory component of this pathway is neither enhanced nor reduced by interneuron activity. The difference between Schaffer collateral and temporoammonic LTD in terms of the involvement of inhibition may be due to the fact that stimulation in SLM may activate GABAergic pathways only disinaptically, in a forward fashion (Empson and Heinemann 1995), whereas stimulation in SR to activate the Schaffer collaterals can also directly activate axons of CA1 interneurons (e.g., see Arai et al. 1995; Lambert et al. 1991). The differences in temporal patterning of excitation and inhibition in the Schaffer collateral and temporoammonic pathways may play a role in the differential responses to LFS shown by these two pathways.

The induction of homosynaptic LTD in other pathways requires an increase in intracellular Ca<sup>2+</sup> concentration, either by influx through NMDA receptors (Cummings et al. 1996;
fibers closer to the subiculum (Witter et al. 1989). It should
molecular layer (Witter et al. 1989). The temporoammonic
layer, whereas the MPP terminates in the middle third of the
modistal axis of the dendrites of the granule cells of the dentate
granule cells, it should be noted, are recorded independently in vivo or in vitro by virtue of the
Malenka 1993). The LPP and MPP can be activated and
NMDA receptor activation for LTP, at least in vivo (Bramham
et al. 1997), although in vitro studies show no difference in
temporal expression or AP5 sensitivity (Dvorak-Carbone and
Schuman, unpublished data). However, this question would
likely best be resolved by in vivo experiments where the lateral
and medial temporoammonic fibers could more unambiguously
be stimulated independently.

SLM, the terminal field of the temporoammonic pathway,
receives a strong cholinergic input from the septum (Matthews
et al. 1987), and mAChR activation has been implicated in
some forms of hippocampal LTD (Auerbach and Segal 1996).
Because stimulation directly in SLM could have activated
septal axons remaining in the slice, it was important to show
that the LTD observed was not due to release of ACh from
septal afferents. Temporoammonic LTD was unaffected by
application of the mAChR antagonist atropine (Fig. 5), show-
ing that the observed depression was not due to the activation
of cholinergic inputs.

When studying synaptic depression, it is important to show
that the effect of LFS on the synaptic response does not simply
reflect damage to the synapses or general degradation of the
slice. To monitor the health of the slice, we applied test stimuli
to the Schaffer collateral pathway alternately with the test
stimuli applied to the temporoammonic pathway and observed
no change in the Schaffer collateral response while the tem-
poroammonic response was depressed (Fig. 2A). The ability to
reverse synaptic depression with HFS can also counterindicate
synaptic rundown or poor slice health (Dudek and Bear 1993;
Mulkey and Malenka 1992). When we applied HFS to a
depressed temporoammonic pathway, we observed a partial
recovery of the response to a level between the depressed level
and the original baseline; repeated application of HFS brought
the response back up to the original baseline, suggesting that
the depressed temporoammonic pathway had not suffered
some nonspecific damage (Fig. 6). Furthermore, HFS applied
to the depressed pathway in the presence of bicuculline re-
sulted in complete recovery and potentiation of the response
above the original baseline level (Fig. 6).

The requirement for multiple applications of HFS to bring
the depressed temporoammonic response back to baseline after
LTD is consistent with the lack of LTP seen in naive slices. In
agreement with a previous report (Colbert and Levy 1993), we
were able to potentiate the temporoammonic response in naive
slices by HFS or TBS only in the presence of bicuculline. Com-
pared with the Schaffer collateral response, the temporo-
ammonic field response is fairly small to begin with and might
therefore require disinhibition before it can be potentiated;
indeed, it has been shown that LTP cannot be induced in this
pathway, even in the presence of bicuculline, if the initial
response is too small (Colbert and Levy 1993). [LTP of the
temporoammonic pathway in the slice preparation in the pres-
ence of intact inhibition has been shown only in a situation
where the temporoammonic input was stimulated so as to elic-
it a population spike recorded in stratum pyramidale (Doller and
Weight 1985); we never observed population spike activity in response to temporoaommonic stimulation.] The LTP that was induced by HFS of the temporoaommonic pathway was dependent on the activation of NMDA receptors (Fig. 7), just like LTP in many other hippocampal pathways (Bliss and Collingridge 1993).

The entorhinal cortex is not the only brain region to send a projection to SLM of area CA1. Fibers from nucleus reuniens thalami (Doolan-Van Der Wiel and Witter 1996; Wouterlood et al. 1990), the amygdala (Petrovich et al. 1997), and area TE of inferotemporal cortex (Yukie and Iwai 1988) also terminate in SLM, raising the possibility that activity in these areas might also serve to modulate or gate information flow through the trisynaptic circuit. It is worth noting that extracellular stimulation electrodes placed in SLM may well activate these fibers as well as temporoaommonic axons.

The function of the temporoaommonic pathway and of other inputs to SLM is not yet well understood. In vivo studies suggest that the temporoaommonic input plays a role in the generation of θ oscillations (Buzsáki et al. 1995) and 40-Hz oscillations (Charpak et al. 1995); models of the hippocampus as a heteroassociative learning network include the temporoaommonic pathway and the Schaffer collateral pathway as two distinct information-bearing inputs to CA1 (Hasselmo and Schnell 1994). The inhibition activated by temporoaommonic input may serve to gate the output of the hippocampus (Dvorak and Schuman 1997; Empson and Heinemann 1995). Temporaommonic activity has also been shown to be capable of modulating the induction of LTP at the Schaffer collateral input to CA1 (Levy et al. 1998); it will be interesting to examine the impact of plasticity of the temporoaommonic pathway on this heterosynaptic modulatory effect.

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