Long-Term Potentiation Disrupts Auditory Gating in the Rat Hippocampus

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The consequence of long-term potentiation (LTP) of hippocampal commissural inputs was investigated in an auditory gating paradigm. Auditory evoked potentials (AEPs) were recorded in the CA3₁ region of the hippocampus of rats anesthetized with chloral hydrate. Two tones were delivered 0.5 sec apart; in this paradigm, the second AEP is diminished compared to the first. Electrical stimulation was applied to hippocampal commissural fibers to generate field potentials and population spikes which were recorded at the same site as the AEPs. LTP of the commissural input (initiated by three trains of 250 Hz/1 sec stimulation) was associated with changes in the AEPs: on average, the response to the first tone decreased and the response to the second tone increased, resulting in the disruption of auditory gating. When high-frequency stimulation of the commissural input failed to result in LTP, no effect on the AEPs was seen. If 3-(2-carboxypiperazin-4-yl)-propyl-L-phosphonic acid (CPP; 6 mg/kg, i.p.), an antagonist to the NMDA subclass of glutamate receptors, was administered prior to high-frequency stimulation, LTP induction was blocked and AEPs were not affected. Finally, reversal of LTP, achieved by high-frequency stimulation of CA3 input that was heterosynaptic to the particular commissural fibers at which the LTP was originally generated, caused disrupted auditory gating to return to normal. A model of reciprocal LTP and heterosynaptic depression of commissural and auditory input pathways is proposed to explain these findings.

[Key words: long-term potentiation (LTP), plasticity, hippocampus, CA3, auditory processing, sensory gating, rat, auditory evoked potentials]

The role of the hippocampus in the information processing required for learning and memory has been extensively studied. It is known that the hippocampus serves as a multi-modal association cortex, bringing together diverse sensory input (Swanson, 1983). Hippocampal neurons are responsive to complex spatial cues, a characteristic which is consistent with a role for the hippocampus in spatial learning (O'Keefe and Nadel, 1978; Kubie and Ranck, 1983; McNaughton et al., 1983). At the cellular level, hippocampal long-term potentiation (LTP) has been

implicated as a mechanism underlying learning and memory (Swanson et al., 1982; Teyler and Discenna, 1984; Morris, 1990). Alternatively, the information processing that precedes memory encoding may require LTP (DeJonge and Racine, 1985; Squire, 1987).

Auditory information is part of the sensory spectrum that the hippocampus acts upon (Berger et al., 1976; Rose, 1983; Brankack et al., 1986; Bickford-Wimer et al., 1990; Edeline et al., 1990). This information relayed to the hippocampus from several brain regions, including the medial septum (Harrison et al., 1988; Miller and Freedman, 1993) and the auditory responsive region of the entorhinal cortex (Stafekhina and Vinogradova, 1975; Vayssettes-Courchay and Sessler, 1983; Foster et al., 1988).

In general, auditory processing can be divided into two categories: (1) that occurring in the classical lemniscal system, which primarily involves signal frequency, intensity, and timing discriminations (Kelly, 1991); and (2) that occurring in extra-lemniscal pathways, which exhibits plasticity to sounds of behavioral significance (Weinberger and Diamond, 1987; Weinberger et al., 1990). Hippocampal processing is extra-lemniscal (Jirsa et al., 1992). Thus, learning changes the response of hippocampal neurons to auditory stimuli which have acquired behavioral significance (Berger et al., 1976; Edeline et al., 1990). Since these changes must be the result of learning-related modifications in the selective weighting of inputs to the hippocampal neurons, changes in synaptic strength induced by artificial means (e.g., LTP stimulation) might also be expected to modify hippocampal processing of auditory stimuli.

The type of hippocampal auditory processing we have studied is shown in Figure 1, which illustrates a mid-latency (N40) evoked potential that can be recorded in the hippocampus of a rat 40 ± 10 msec after a 3 kHz, 70 dB tone and which shows diminished amplitude if an identical tone is presented 500 msec later. This phenomenon is termed auditory gating, and may relate to models of hippocampal function involving the filtering out of irrelevant stimuli (Douglas, 1972; Solomon, 1977). Auditory gating is reflective of processing in the central extra-lemniscal pathway and is not observed in nuclei of the central lemniscal pathway (Bickford-Wimer et al., 1990; Bickford et al., 1993).

How might LTP interact with auditory gating in the hippocampus? The impact of LTP has been difficult to determine in terms of a specific *in vivo* consequence to an animal (Eichenbaum and Otto, 1993). Yet, assuming that alterations in the strengths of synaptic input occur *in vivo*, such changes should affect hippocampal function in some manner. In this study, we investigated the effect of LTP on auditory gating of the N40

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Figure 1. Examples of N40 potentials (marked by dots) recorded in CA3_b, elicited by paired auditory stimuli that are separated by 500 msec (marked by arrows). The upper set of potentials is representative of baseline auditory gating. A T/C ratio of 0.5 is considered to be the level above which gating is lost (see Materials and Methods). The lower set of potentials illustrates a loss of auditory gating resulting from a decrease in the conditioning response amplitude and an increase in the test response amplitude.

potential recorded in the hippocampus of the rat. In common with LTP, auditory gating is a process that is reflected in extracellular potentials and can be measured electrophysiologically at the site of LTP generation. The paradigm involves fewer dimensions than learning and memory studies and is more closely associated with the substrate upon which LTP acts: excitatory input to hippocampal pyramidal cells and interneurons.

Materials and Methods

Animals and surgery. Thirty-four adult male Sprague-Dawley rats (250–350 gm; Harlan Laboratories, Indianapolis, IN) were recorded during the course of this study. The animals were anesthetized with chloral hydrate (400 mg/kg, i.p.) which had been prepared in a buffered solution of 100 mM NaCl and 50 mM HEPES (final pH 7.2) and stored at 4°C until use. Chloral hydrate was selected as the anesthetic because it preserved the auditory response very well, whereas other anesthetics tried (pentobarbital and urethane) did not. To extend the period of stable anesthesia, the metabolism of chloral hydrate to trichloroacetic acid was blocked by the administration of pyrazole, an inhibitor of alcohol dehydrogenase (Cooper and Friedman, 1958; Miller et al., 1993). Pyrazole was injected intraperitoneally at a loading dose of 200 mg/kg, with 30 mg/kg supplements at 30 min intervals.

The level of anesthesia was carefully monitored throughout the course of the experiment, and was adjusted with supplemental doses of chloral hydrate as necessary. The anesthesia level was judged to be inadequate when there was response to toe pinch and/or presence of the corneal reflex to touch with dry cotton wisp. A state of excessive anesthesia was determined to exist when the corneal reflex was no longer present to the application of a wet cotton wisp. Based on observations from previous work (Miller et al., 1992, 1993), and also observed here, conditions of either too much or too little anesthesia resulted in variable changes in the size of hippocampal field potentials and auditory N40, and consistently disrupted auditory gating. However, when a stable and appropriate level of anesthesia was maintained these problems were not observed (Miller et al., 1993; see Results).

Electrophysiology. The rats were secured in a stereotaxic apparatus, adjustments were made to ensure that the skull was flat, and after removal of small sections of the skull and dura, a recording electrode (tungsten, coated with non-conducting varnish; 3 to 5 MΩ resistance) was lowered into the hippocampus (from bregma, −3.8 mm AP, 3.6 mm ML). A stimulating electrode (tungsten, coated with nonconducting varnish; 0.25 MΩ resistance) was lowered to one of three different stereotaxic locations to stimulate commissural input to the recording electrode site: (1) in the ventral hippocampal commissure (−1.8 mm AP, 1.0 mm ML, and 2.7–2.9 mm DV; see Swanson, 1992), (2) in the contralateral CA3 anterior to the plane of the recording electrode (−1.8 mm AP, 1.0 mm ML, and 3.4–3.5 mm DV), or (3) in the contralateral CA3 homotopic to the recording electrode site (−3.8 mm AP, 3.7 mm ML, and 2.9–3.4 mm DV). Stereotaxic locations of recorded groups of cells was used as an aid to correct placement of the recording electrode. The initial landmarks used were the field potential induced by commissural stimulation and the presence of neurons firing with the complex spike characteristic of hippocampal pyramidal cells, first encountered at the depth corresponding to the CA1 layer (usually 1.9–2.2 mm from the dura). Extracellular recordings of action potentials were amplified by a high-input impedance amplifier and then further amplified and displayed on the oscilloscope. For the action potential recordings, the bandpass filter was set to limit the response to 300–10,000 Hz. Below the CA1 pyramidal layer, the potentials evoked by stimulation of the commissure were characteristic dendritic negativities until the CA3 pyramidal layer was reached at depths generally > 2.9 mm. Complex spikes of CA3 pyramidal cells were always recorded, but more diagnostic was the distinctive antidromic response to commissural stimulation found in CA3 but not in CA1 (Fig. 2). The electrode was determined to be in the pyramidal cell layer of CA3_b and not CA3_c or CA3_a, if, while lowering the electrode, (1) the dentate gyrus granule cell layer was not encountered, and (2) pyramidal cells were recorded in a discrete band and not in a more continuous dorsal/ventral band corresponding to CA2/CA3_a.

Sufficient negative (cathodal) current of 150 μsec pulse width was administered to the stimulating electrode to generate a CA3 population spike and/or a field potential, each of at least 1 mV amplitude. The

Figure 2. Spontaneous pyramidal cell complex spikes and potentials evoked in the hippocampal pyramidal cell layers by electrical stimulation of commissural fibers recorded in areas CA1 (*A*) and CA3 (*B*). 1, Stimulation artifact; 2, antidromic population spike; 3, orthodromic population spike; 4, positive-going field potential. Note that the time scale for the action potentials is different between *A* and *B*, and that the voltage scales are different in all cases.

range of current required was 25–300 μ A (Table 1). In five cases it was not possible to elicit a population spike with commissural stimulation prior to LTP, even though a large positive field potential was generated. A series of at least six test pulses was delivered to establish the mean field potential and population spike amplitude prior to high-frequency electrical stimulation. The variability in the population spike amplitude generally ranged from 5 to 20%, and the variability in the EPSP amplitude was 3–20%. With the same current used to record the baseline data, three trains of 250 Hz, 1 sec pulses, each separated by 5 sec, were then delivered to the stimulating electrode. This stimulation protocol was developed in an attempt to reliably achieve a significant degree of LTP. More physiologically relevant protocols were also successful (e.g., Rose and Dunwiddie, 1986), but less reliable and not as likely to yield as large a degree of potentiation. Potentiation of the electrically evoked potential was then monitored by administering a trial of at least six test pulses. Potentiation was deemed to have occurred if a two-tailed *t* test of a series of population spike or positive field potential amplitudes revealed a significant increase between those values and the baseline values ($p < 0.05$). LTP was deemed to have occurred if the potentiation was observed across all trials during the period of at least 1 hr (Racine et al., 1983; Linden, 1994) and if successive measures revealed a stable potentiation during the 1 hr long period (i.e., no significant decrease between successive measurements of the electrically evoked potential). If potentiation was induced that was not stable, a second high-frequency train of electrical stimuli was administered in an attempt to achieve LTP

Table 1. Stimulator currents required to generate a field potential or population spike of 1 mV in amplitude

Stimulator placement	Subsequent LTP status ^a	Current mean ($\pm$ SD, μ A)	N	Current range (μ A)
VHC ^b	(+)	81 $\pm$ 32	8	40–140
	(–)	143 $\pm$ 137	3	50–300
Anterior CA3	(+)	73 $\pm$ 29	11	25–115
	(–)	185	2	90–300
Homotopic CA3	(+)	57 $\pm$ 17	5	40–90
	(–)	50	2	40–60

^a LTP of the population spike.

^b Ventral hippocampal commissure.

(see Results). This approach was successful in three of three rats, which were then included in the +LTP data set.

Once the post-LTP response had stabilized, the variability of the population spike amplitudes, averaged over 5 min intervals of time (similar to the time period of the baseline collection), ranged from 3% to 32%, or 0.6–3-fold the variability seen in the pre-LTP period (paired, within-animal observations). The variability in the field potential amplitudes ranged from 2% to 18%, or 0.6–2.2-fold the variability seen in the pre-LTP period.

The auditory evoked potentials were elicited by presentation of tones (3000 Hz, 70 dB SPL, 10 msec duration) through hollow stereotaxic earbars. The auditory stimulus intensity was selected to fall in the middle of a plateau. At intensities above approximately 50 dB the amplitude of the evoked potential shows no significant change with intensity level (unpublished data), and below 90 dB the startle mechanism is not a confounding factor (Keith et al., 1991).

Two tones, separated by 500 msec, were presented every 10 sec. Signals were filtered such that only electrical activity with frequencies between 0.1 and 1000 Hz were recorded. Sixteen pairs of tones were presented in each trial and an average waveform was constructed from the digitized components of the 16 N40 responses. Test/conditioning (*T/C*) ratios were calculated from the average waveform. The mean *T/C* ratio for a specific period of analysis represents the mean of all the *T/C* ratios calculated for each trial during that period. Historically, a *T/C* ratio of >0.5 has been associated with psychosis in humans (Adler et al., 1982; Freedman et al., 1987). Similar *T/C* ratios are seen following the administration of drugs at doses that are known to have psychotomimetic effects in rats (Adler et al., 1986; Miller et al., 1992). A *T/C* ratio of 0.5 is >2 SD units above the mean value of 0.25–0.35 found for controls in previous studies (Miller et al., 1992, 1993) and is considered to be the value above which gating is lost. The minimum time separating trials of auditory evoked potentials was 5 min. A minimum of four trials was collected prior to high-frequency electrical stimulation to confirm that a given animal's auditory gating was stable. Any rat which failed to show consistent auditory gating was excluded from further study. Viral infections or, as was explained earlier, cyanosis from too much anesthesia can lead to lack of gating in our paradigm. In addition, approximately 10% of the rat subjects fail to gate the N40 for

Table 2. LTP of the population spike or the field potential depends on stimulator placement

Stimulator placement	LTP of population spike ^a (mean % control $\pm$ SD)	LTP of field potential (mean % control $\pm$ SD)
VHC	210 $\pm$ 170	228 $\pm$ 92*
Anterior CA3	327 $\pm$ 232	168 $\pm$ 68
Homotopic CA3	264 $\pm$ 138	118 $\pm$ 16

^a Values do not include those experiments in which no prior population spike was recorded.

*Value is significantly different from the others in this column, $p < 0.03$.

unknown reasons; those rats were excluded as well. Following high-frequency electrical stimulation, trials of auditory evoked potentials and electrically evoked potentials were conducted. The minimum time interval separating a trial of auditory evoked potentials from a trial of electrically evoked potentials was 1 min, and the maximum interval was usually <10 min.

Statistics. Data are expressed as mean $\pm$ the standard deviation, unless otherwise specified. Significant differences between values obtained in an individual rat, before and after treatment, were determined using an unpaired, two-tailed, *t* test comparing all the values before treatment to all the values after treatment ($n > 4$ in all cases for *T/C* ratio; $n > 6$ in all cases for electrically evoked potentials). Significance was set at $p < 0.05$. Thus, a statement that no potentiation was observed in four rats indicates that in no case was there a significant difference in the before and after values in those four rats. In cases of successive treatments in the same rat, the significance of a treatment was always established as compared to the baseline (control) condition for that particular rat. In no case was a statistical test applied to determine if the *T/C* ratio was significantly different than the value of 0.50, above which gating is considered to be lost.

The data were analyzed for a specified group of rats by computing mean values for the before and after treatment conditions, pairing those values for each rat, and then applying a paired, two-tailed *t* test to assess the significance level of the data across the group. Thus, for all cases in which data is cited for a group of rats, the *t* test that was applied was paired. Significance was set at $p < 0.05$.

Results

Electrical and auditory stimulation

The auditory and electrically evoked potentials were recorded in CA3_b, a region which lies ventral and lateral to the buried blade of the dentate gyrus, but medial to the flexure of CA3. CA3_b receives virtually all of its commissural input from the contralateral CA3_b (Voneida et al., 1981), and thus, is relatively free of the potentially confounding influence of dentate efferents (Steward et al., 1990) that project across the ventral hippocampal commissure to other regions of the hippocampus (Voneida et al., 1981). Previous work had revealed a population of auditory responsive pyramidal cells in the CA3_b region, as well as robust N40 auditory evoked potentials (Bickford-Wimer et al., 1990).

Three different stimulator placements were used: (1) in the ventral hippocampal commissure, (2) in the contralateral CA3 anterior to the recording electrode, and (3) in the contralateral CA3 homotopic to the recording electrode site. Stimulus-evoked potentials recorded in response to the three stimulator placements were similar in form, although there were some differences in stimulus thresholds (Table 1). LTP of the field potential and/or population spike was achieved in 28 of 31 rats studied. In four rats, the peak amplitude of the positive field potential was increased without a corresponding potentiation of the population spike, and on two occasions the population spike increased without a corresponding potentiation of the positive field potential. Stimulator placement had an influence on whether the positive field potential or the population spike was more affected by high-frequency stimulation. The positive field potential was potentiated to the greatest degree following stimulation of the ventral hippocampal commissural fiber tract placement (one-way ANOVA, $p < 0.03$; Table 2). The population spike showed a trend to be potentiated to the greatest degree by stimulation of the anterior CA3 placement, but this trend did not reach statistical significance. There was no correlation between the magnitude of population spike increase and the positive field potential increase ($r = 0.03$, $p > 0.8$), a finding replicating previous work that showed a correlation between potentiation of the population spike and the negative-going dendritic field potential but no correlation with the positive field potential recorded at the cell soma (Rose et al., 1993).

Auditory-evoked potentials to paired tones were recorded at the same site and through the same electrode as the electrically evoked potentials, although not at the same time. The ratio of the test response to the conditioning response (*T/C* ratio) was calculated for each of four trials and stable auditory gating was confirmed prior to administering a high-frequency train of stimuli through the stimulating electrode (Fig. 1). There was a weak positive correlation between the conditioning and test amplitudes under baseline conditions ($r = 0.46$, $p < 0.001$). For the 31 rats studied in this series of experiments, the mean baseline *T/C* ratio was 0.28 ± 0.08 .

The effect of LTP on auditory gating

The development of LTP significantly disrupted auditory gating (Fig. 3). The field potential and population spike were monitored for 5 min and then auditory evoked potentials and electrically evoked potentials were alternately collected for at least 1 hr following the high-frequency electrical stimulation of contralateral/commissural input to CA3_b. In the 28 rats showing LTP (i.e., potentiation for periods > 1 hr; see Materials and Methods), the mean change over a 1 hr LTP period was $+275 \pm 192\%$ in the population spike ($p < 0.0001$), $+177\%$ (80% in the field potential amplitude ($p < 0.0001$) and $+0.48 \pm 0.40$ in the *T/C* ratio ($p < 0.0001$). In contrast, potentiation that was not stable (see Materials and Methods) did not result in disruption of auditory gating (as shown for the *T/C* ratio and population spike in Fig. 4). Within individual rats the variability of the *T/C* ratio between trials went up, on average, fourfold during LTP. This large post-LTP increase in variability of *T/C* ratio derived from an increase in variability of both the conditioning (1.4-fold) and the test (1.9-fold) amplitudes, as well as an increase in variability of the relationship between the conditioning and test amplitudes.

Although the mean *T/C* ratio over four consecutive trials remained perturbed for the duration of the LTP, the auditory gating frequently showed intermittent normalization in single trials (Fig. 4), when the *T/C* ratios fell to <0.50. Intermittent normalization has also been observed in experiments investigating the pharmacological perturbation of auditory gating (Miller et al., 1992) and in part may result from shifts in the populations of neurons responding to the tone (Miller and Freedman, in press). However, this normalization was never observed for more than two consecutive trials, which distinguished the LTP period from the pre-LTP period. The increased variability discussed above, and illustrated in Figure 4, could be interpreted as simply an increase in noise in the system following LTP induction; however, the intermittent periods of normalization after LTP were always bracketed by extended periods of gating disruption. It does not seem likely that the increase in mean *T/C* ratio which occurred during LTP resulted from the interaction of the variability with a floor effect because the lowest *T/C* ratio during LTP was still higher than the lowest *T/C* ratio encountered in each rat during baseline conditions (in all cases, including that presented in Fig. 4).

The aspect of LTP that correlated with the loss of gating of the N40 was the magnitude of the population spike increase ($r = 0.6$, $p < 0.0007$). In contrast, there was no correlation between gating loss and enhancement of the positive field potential potentiation ($r = 0.17$; $p > 0.3$). There was a positive correlation between the LTP-induced increase of population spike and the increase in *T/C* ratio (indicating a reduction of gating) for all three stimulator placements, although a significant relationship between the two variables was found only for LTP induced by

Figure 3. The effect of LTP on auditory gating. **A**, A paired *t* test of the *T/C* ratios before and after LTP revealed that the gating loss was statistically significant ($n = 28$; $p < 0.0001$). The *T/C* ratios are graphed as means $\pm$ SEM. **B**, An representative experiment. *Top*, LTP was induced by stimulation of the VHC. *Bottom*, Four consecutive samples of auditory evoked potentials recorded prior to LTP stimulation (*left*) and during LTP (*right*). These data illustrate the transition from test amplitude increase to conditioning amplitude depression which followed successful LTP induction. The elapsed time from the first *BASELINE* N40 evoked potentials shown to the last was 30 min. The elapsed time from the first *+LTP* N40 evoked potentials shown to the last was 15 min.

tetani delivered through the contralaterally placed stimulators (Fig. 5).

In no case did LTP stimulation have an immediate effect on auditory gating. This finding was independent of stimulator placement. From the time of the peak potentiation observed within the first 10 min following the high-frequency train, the mean time to onset of the auditory gating loss was 10.5 ± 7 min (range, 4–29 min).

Following LTP, both the N40 conditioning amplitude and test amplitude were significantly altered compared to baseline values ($p < 0.05$; paired *t* test): the conditioning amplitude decreased and the testing amplitude increased. Furthermore, the effect had two phases (Table 3). Initially, the auditory gating was disrupted primarily by a large increase in the test amplitude. These short term values for test amplitude were significantly greater than the test amplitude values at later time points ($p < 0.01$). It was generally the case that, within 5–15 min of the initial disruption of gating, the conditioning amplitude depression became more pronounced, although overall this change was not significantly different from the reduction in conditioning amplitude associated with the initial gating loss ($p > 0.05$). Figure 3*B* illustrates such a transition in the conditioning and test amplitudes.

Controls for effects of high-frequency electrical stimulation not related to LTP of the population spike

In three rats, high-frequency electrical stimulation failed to potentiate either the field potential (mean change = $-30 \pm 44\%$; $p > 0.35$) or the population spike (mean change = $-3.7 \pm 5.5\%$; $p > 0.36$). In these cases, the resulting mean change from baseline *T/C* ratio was not significant (-0.02 ± 0.08 , $p > 0.40$; Table 4, group E). In four other rats, only the field potential was potentiated (mean change = $+83 \pm 6\%$; $p < 0.001$; mean change in population spike = $-11 \pm 22\%$; $p > 0.41$). For these animals

also, no significant change from baseline *T/C* ratio was observed after high-frequency electrical stimulation ($+0.07 \pm 0.09$; $p > 0.30$; Table 4, group D).

As a further control for potential nonspecific effects of high-frequency electrical stimulation, three rats received and intraperitoneal dose of 6 mg/kg of the competitive NMDA antagonist CPP, 20 min prior to high-frequency stimulation of the ventral hippocampal commissure (two animals) or anterior CA3 (one animal). Commissural LTP is NMDA dependent (Collingridge et al., 1983; Zalutsky and Nicoll, 1990); therefore, it was possible to block LTP with the prior administration of CPP. In CPP-treated rats, as expected, LTP was not generated by the high-frequency electrical stimulation; in addition, auditory gating was not perturbed. The mean change was $-2.6 \pm 2.3\%$ ($p > 0.15$) in the population spike amplitude, $+10 \pm 37\%$ ($p > 0.50$) in the positive field potential amplitude and -0.04 ± 0.12 ($p > 0.6$) in the *T/C* ratio (Table 4, group F). These data show that the auditory gating loss and the LTP are correlated in that they both require activation of the NMDA receptor in this paradigm. Thus, the CPP data serves as a control for aspects of high-frequency stimulation that are unrelated to activation of the NMDA receptor.

Is it a significant finding that rats which did not develop LTP of the population spike also did not experience a change in auditory gating? Dividing the 34 member experimental population (Table 4) into two groups, those that developed LTP of the population spike and those that did not, and applying one-way ANOVA to the change in *T/C* ratio experienced by the two groups following high-frequency stimulation, the finding was determined to be significant ($F = 17.4$; $p < 0.0002$). In contrast, the same analysis applied to LTP of the positive field potential revealed no relationship to changes in auditory gating ($F = 0.62$; $p = 0.44$).

Figure 4. Time course of an experiment in which the first high-frequency train (delivered at the 20 min time point) elicited a potentiation that was not stable (see Materials and Methods). Disruption of auditory gating (mean T/C ratio > 0.5) occurred only with the development of LTP following the second train (delivered at the 95 min time point). The time course of the potentiation following the second high-frequency train is characteristic of the +LTP experiments. The mean T/C ratios were 0.12 ± 0.11 for the baseline period, 0.44 ± 0.15 for the period following the first train, and 1.25 ± 0.84 for the period following the second train. This finding was replicated in two additional rats.

Figure 5. Correlation between LTP of the population spike and loss of auditory gating for three different stimulator placements. The data set does not include experiments in which there was no population spike prior to LTP. *A*, Stimulator location in the ventral hippocampal commissure. *B*, Stimulator location in the anterior CA3, contralateral to the recording electrode. *C*, Stimulator location in CA3, contralateral and homotopic to the recording electrode. In all cases there was a positive correlation between LTP-induced growth of the population spike and an increased T/C ratio, indicating a reduction in gating. However, these correlations were statistically significant only for the anterior CA3 and contralateral/homotopic stimulator placements.

Table 3. The contribution of conditioning amplitude depression and test amplitude increase to the loss of auditory gating seen with LTP: initial and delayed effects

Elapsed time (min) ^a	Mean change in conditioning amplitude (% control $\pm$ SD)	Mean change in test amplitude (% control $\pm$ SD)
0	-25 ± 30	$+107 \pm 57$
5–60 ^b	-43 ± 20	$+78 \pm 56^*$

^a time since first onset of auditory gating loss. Zero minutes represents only one trial.

^b The 5–60 min time point represents the mean, for each experiment, of all the trials for 60 min following the onset of the auditory gating loss, summed for all experiments in which there was LTP of the population spike ($N = 21$) to generate an overall mean.

* Significantly different from 0 time point, $p < 0.01$.

Reversal of LTP and normalization of auditory gating

Placement of stimulating electrodes in the anterior CA3 and the homotopic CA3 revealed an apparent heterosynaptic depression if high-frequency stimulation was applied alternately to both sites of stimulation. Furthermore, if the second input yielded a poor population spike response while the first yielded a robust population spike response, it was possible to generate LTP at the first input and then reverse it by administering a high-frequency stimulus to the second input, without generating LTP of the second input. Thus, it was possible to use this heterosynaptic stimulation paradigm to first generate LTP, and then return to the baseline condition of no potentiated inputs.

Two stimulating electrodes were lowered, one to the contralateral anterior CA3 and the other to the contralateral CA3 homotopic to the recording electrode. The stimulation site yielding the more sensitive population spike response for a given current intensity was selected as the site for initial LTP generation. Following LTP induction, reversal of the LTP was attempted by applying a high-frequency train (250 Hz, up to 400 μ A, 150 μ sec pulse duration, for 1 sec) to the other commissural stimulator. Complete reversal of LTP was achieved in five of

seven rats for varying amounts of time. In one of the failures, reversal of the original LTP occurred but LTP developed from the second site of high-frequency stimulation, and in the other, no reversal of LTP took place. In the successful reversal experiments, auditory gating was normalized to a mean $T/C < 0.5$ (as defined in Materials and Methods) for the period during which the population spike amplitude was less than or equal to the original baseline value (Fig. 6). The mean time period of successful reversal of LTP was 24 ± 8 min (range, 15–35 min), which covered at least four trials of auditory gating. In individual rats, the T/C ratios during reversal were compared to an equivalent number of trials during LTP. The minimum mean T/C ratio during LTP was significantly greater than the mean T/C ratio during reversal in all five animals ($p < 0.05$). Furthermore, there was no significant difference between the T/C values during reversal and the original baseline T/C values (mean difference, 0.02 ± 0.10 ; range, -0.10 to $+0.14$; $p > 1.0$). Within individual rats, the variability in the T/C ratio decreased from approximately fourfold during LTP to an average of 1.3 times that of the baseline during the reversal period.

Comparison of the mean difference between the electrically evoked positive field potentials during reversal and the original baseline values revealed no significant difference (mean, $-11.7 \pm 16.6\%$; range, -29% to $+10\%$). Comparisons for individual rats indicated no significant change in four rats ($p > 0.3$) and significant reduction in one ($p < 0.005$). Mean population spike amplitudes during reversal were $-22 \pm 37\%$ (range, -58% to $+33\%$) compared to pre-LTP baseline values. Individual comparisons revealed no significant difference for two rats ($p > 0.25$) and a significant reduction in the other three ($p < 0.05$).

Discussion

LTP of commissural input to the hippocampus disrupted auditory gating in a proportional and reversible manner. This effect is unlikely to have resulted from an aspect of high-frequency stimulation unrelated to LTP because (1) when high-frequency stimulation failed to generate LTP, gating was not altered; (2) when LTP was purposely prevented by the administration of an

Table 4. Summary of treatment and results

Group	Treatment	Result	N
A	High-frequency stimulation	LTP of population spike LTP of positive field potential Loss of auditory gating	18
B	As above	LTP of population spike No LTP of positive field potential Loss of auditory gating	2
C	As above	LTP of population spike LTP of positive field potential No change in auditory gating	4
D	As above	No LTP of population spike LTP of positive field potential No change in auditory gating	4
E	As above	No LTP of population spike No LTP of positive field potential No change in auditory gating	3
F	CCP before high-frequency stimulation	No LTP of population spike No LTP of positive field potential No change in auditory gating	3

Figure 6. Example of a reversal experiment. LTP was generated by stimulation of afferents from the contralateral CA3 homotopic to the recording site, and then reversed by high-frequency stimulation of fibers originating in the anterior CA3. *Top*, Averages of stimulus-evoked potentials. A large increase in the orthodromic population spike was observed during LTP, but was returned to the pre-LTP amplitude by heterosynaptic stimulation. The antidromic population spike remained stable throughout all manipulations. *Bottom*, Averages of auditory evoked potentials. Gating of N40 was disrupted following LTP induction, but returned to baseline levels following LTP reversal. The N40 evoked potentials are four consecutive traces from each of the respective time periods. The elapsed time from the first *BASELINE* N40 evoked potentials shown to the last was 18 min. The elapsed time from the first *+LTP* N40 evoked potentials shown to the last was 15 min. The elapsed time from the first *REVERSAL OF LTP* N40 evoked potentials shown to the last was 15 min.

NMDA antagonist, gating was unchanged following high-frequency stimulation; and (3) high-frequency stimulation itself was used to normalize gating that had previously been perturbed by LTP.

Gating loss was correlated with an LTP-induced increase in the population spike, but not the positive field potential, recorded in the CA3 pyramidal cell layer. Population spikes are summed action potentials of pyramidal cells (Andersen et al., 1971) and therefore, are a reflection of postsynaptic excitation. Extracellular field potentials are thought to reflect excitatory and inhibitory synaptic currents generated at postsynaptic sites on pyramidal cells (Schlag, 1973; Leung, 1979; Di et al., 1990). Electrical stimulation of the commissure activates both excitatory and inhibitory synaptic currents within a few milliseconds of each other (Buzsaki and Eidelberg, 1982); the resulting positive and negative currents sum, tending to cancel each other out. Due to this interaction between positive and negative currents, the peak magnitude of the extracellularly recorded positive field potential is not likely to reflect changes in excitatory input to pyramidal cells in a graded manner. In contrast, the population spike should provide more of a graded reflection of excitatory input to the pyramidal cells because the faster frequency action potential currents are not affected by the slower frequency field potential currents. This suggests that changes in synaptic strength will be more accurately represented by alterations in the population spike rather than in a field potential which is recorded distant from the site of synaptic input.

Theoretically, LTP of the excitatory synapses carrying the tone input should cause the N40 conditioning amplitude to increase in size. Rogan et al. (1993) have demonstrated such a relationship between tone evoked potentials and LTP of medial geniculate afferents to the amygdala. In the present work, LTP of hippocampal commissural connections resulted in a decrease in N40 conditioning amplitude was observed. However, as was

mentioned in the introductory section, commissural synapses are not likely to be carrying the auditory signal to the hippocampus. Rather, entorhinal cortex afferents are thought to be the primary input pathway for auditory information (Foster et al., 1988). Auditory signals may reach CA3 indirectly via the dentate gyrus, or via a direct projection (Yeckel and Berger, 1990; Colbert and Levy, 1992).

One mechanism by which commissural LTP could decrease the conditioning amplitude is by causing heterosynaptic depression of the perforant path synaptic response. Others have observed long-term synaptic depression in the perforant path (Pang et al., 1993) and negative heterosynaptic interactions between commissural and perforant path inputs in CA3 (Tomasulo and Ramirez, 1993). This is a prediction that can be tested in the future by looking for depression of the population spike evoked by perforant path stimulation following LTP of commissural fibers. Assuming that heterosynaptic depression of the perforant path is involved in depression of the conditioning (first tone) response, why does the amplitude of the test (second tone) response increase?

Previous work has shown that interneuronal excitation in the 500 msec following the first tone correlates strongly with the diminished N40 response to the second tone (Miller and Freedman, in press). Current evidence suggests that the excitation of interneurons by the tone does not occur via feedforward activation by pyramidal cells (Miller and Freedman, in press). Rather, the excitation of interneurons by the tone must originate from an external source such as the perforant path. LTP of commissural input to interneurons could cause heterosynaptic depression of monosynaptic or disynaptic perforant path input to interneurons, which would diminish the interneuron response between the tones. This would result in an increased N40 response to the second tone. While most studies of heterosynaptic depression have been carried out in pyramidal cells (for a review, see Lin-

LTP OF 1. = HETEROSYNAPTIC DEPRESSION OF 2.

REVERSAL OF LTP 1. = REVERSAL OF DEPRESSION 2.

Figure 7. A schematic model of the synaptic contacts likely to be important to the effect of commissural LTP on auditory gating. Stimulation of commissural input 1 generates LTP at synapse 1 for both the pyramidal cell and the interneuron. The LTP also causes heterosynaptic depression of perforant path input to these neurons (2), resulting in the depression of N40 conditioning amplitude. The perforant path input refers to either the monosynaptic connection from the entorhinal cortex or the disynaptic connection via the dentate and the mossy fiber system. Heterosynaptic depression of the perforant path input to the interneuron prevents the inter-tone excitation of the interneuron that normally inhibits the pyramidal cell synaptic potential evoked by the second tone; thus, the N40 test potential increases and auditory gating is lost. The reciprocal connections between the pyramidal cell and the interneuron are not shown. To reverse the auditory gating loss, a high-frequency stimulus is applied to commissural input 1'. Reversal of the LTP at synapse 1, without generating LTP at synapse 1', reverses the heterosynaptic depression of the perforant path inputs to the pyramidal cell and the interneuron. Auditory gating then returns to normal.

den, 1994), long-term heterosynaptic depression has been demonstrated in GABAergic interneurons in the hippocampus (Reece and Redman, 1992), as well as in other brain regions (Kombian and Malenka, 1994). In addition, heterosynaptic depression of perforant path input to interneurons has been implicated in the response of the dentate to commissural tetanus (Tomasulo and Ramirez, 1993).

That synapses on different cell types may be involved in the changes in the conditioning versus test amplitudes is supported by a clear separation of the timing of the changes in some of the experiments (Table 3, Fig. 3B). The initial consequence of LTP induction was to increase test N40 amplitude while, in some cases, conditioning N40 amplitude remained unchanged (Fig. 3B). This transition is consistent with our hypothesized loss of interneuron activation by the perforant path and the resulting loss of inhibitory control of the test N40. Next, the conditioning amplitude decreased and the test amplitude decreased slightly also (although it did not return to baseline values). This transition fits well with a decreased perforant path input to pyramidal cells in response to both the first and second tones.

A possible model to explain the effect of commissural LTP, and its reversal, upon hippocampal auditory gating is shown in Figure 7. In other contexts, all of the interactions proposed in Figure 7 have been reported by others. From a condition of LTP at one synapse, it has not only been demonstrated that LTP at a heterosynaptic site (e.g., synapse 1') can introduce depression of the LTP at the first synapse (Levy and Steward, 1979; Christie

and Abraham, 1992; Kerr and Abraham, 1993), but also that it is possible to induce depression of the LTP without getting LTP at the most recently tetanized synapse (Bradler and Barrionuevo, 1990). In addition, there is data demonstrating that depression at an unstimulated synapse (e.g., the perforant path) can be reversed if the LTP causing the heterosynaptic depression is reversed by tetanus of yet another heterosynaptic input (Bradler and Barrionuevo, 1990).

Although input from the entorhinal cortex may be necessary for the response of the hippocampus to tones, other facilitatory inputs are important as well (Harrison et al., 1988; Luntz-Leybman et al., 1993; Miller and Freedman, 1993). Heterosynaptic depression of another facilitatory input could have the same auditory gating effect as the perforant path depression proposed here.

Understanding the significance of the current findings in the context of a behaving animal depends upon the physiological relevance of LTP itself and whether or not long-term synaptic plasticity is related to information processing and/or learning and memory. In addition, although the effect of LTP upon auditory gating is not an artifact of high-frequency electrical stimulation, there may still be aspects of the stimulation protocol that are pertinent when assessing the physiological relevance of the results. The electrical stimulation is broad and nonspecific, characteristics which must certainly differ from the synaptic distribution of learning-induced changes. The hippocampus is extensively affected by the commissural LTP generated in this study, and therefore, the cells responding to the tone input and those experiencing LTP are likely to overlap. In a freely behaving animal, direct parallels with such an experimental outcome are likely occur only under a limited set of circumstances. Learning that is specifically related to the tone would, in all probability, affect the same cells involved in gating the response to the tone. Otherwise, situations in which cells involved in learning might fortuitously overlap with those involved in auditory gating would seem to be limited to conditions of information "overload" or involving hippocampal pathological conditions, such that only a small amount of hippocampal tissue would be available for processing functions.

If cells involved in auditory gating should experience auditory gating loss resulting from learning processes or from LTP of the commissural input, there are likely to be some measurable behavioral consequences in the behaving animal. As described earlier, a loss of auditory gating is correlated with the administration of psychotomimetic drugs in rats and with psychosis in humans, some of the symptoms of which are auditory in nature. However, it is not known how many different regions of the brain must experience the auditory gating loss to cause the auditory-specific features of psychosis. At least two other brain regions are known to exhibit auditory gating [the medial septum (Miller and Freedman, 1993) and the brainstem reticular formation (Bickford et al., 1993)]; it is probable that other extra-lemniscal auditory regions do as well. Here, we have attempted to specifically disrupt auditory processing in the hippocampus, and the behavioral sequelae are likely to be more limited than if gating in all of the extra-lemniscal systems was disrupted. Sakurai (1990) has proposed that the hippocampus is important for initiating motor response to sounds; if so, then loss of hippocampal auditory gating caused by commissural LTP might be expected to alter the motor response to repetitive sounds. Alternatively, the auditory gating disruption may interact with the place cell function of the hippocampus (O'Keefe and Nadel,

1978; Breese et al., 1989; Wilson and McNaughton, 1993), making the spatial attribution of sound less rapid or accurate.

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