ELSEVIER

Brain Research 780 (1998) 95–101

BRAIN RESEARCH

Research report

Induction and transient suppression of long-term potentiation in the peri- and postrhinal cortices following theta-related stimulation of hippocampal field CA1

Graham Cousens, Timothy A. Otto *

Program in Biopsychology and Behavioral Neuroscience, Department of Psychology, Rutgers University, New Brunswick, NJ 08903, USA

Accepted 16 September 1997

Abstract

During behavioral events associated with periods of likely mnemonic processing, CA1 pyramidal cells in rats typically discharge repetitively in either high-frequency bursts ('complex spikes') or single spikes, both of which are tightly phase-locked to the hippocampal theta rhythm. Interestingly, patterned stimulation which mimics the repetitive, learning-related complex spike discharges are optimal for inducing long-term potentiation (LTP) of excitatory field potentials in CA1, and patterned stimulation which mimics the theta-related single action potentials results in a robust and lasting depotentiation at these same synapses. The aim of the present study was to determine the extent to which these physiologically-relevant patterns of hippocampal stimulation have similar effects on synaptic efficacy in the monosynaptic projection from CA1 to the perirhinal and postrhinal cortices (PRh), areas thought to play a prominent role in many forms of learning and memory. Single-pulse stimulation of CA1 evoked a small amplitude, short latency population excitatory postsynaptic potential (EPSP) in the PRh. Theta-burst stimulation (TBS; $n = 8$) delivered to CA1 reliably potentiated the PRh EPSP slope for at least 30 min. Theta-pulse stimulation (TPS; 5 Hz; $n = 4$) delivered to CA1 5 min after TBS substantially but transiently suppressed EPSP slope relative to that of potentiated control preparations. Collectively these data suggest that theta-related patterns of hippocampal activation can reliably induce and transiently suppress LTP in PRh, and are consistent with the notion that behaviorally-relevant, theta-modulated patterns of CA1 unit activity may result in both long- and short-term alterations of synaptic strength within their rhinal cortical targets. © 1998 Elsevier Science B.V.

Keywords: Long-term potentiation (LTP); Rhinal cortex; Perirhinal; Depotentiation; Hippocampus

1. Introduction

The rhinal cortical region (perirhinal, postrhinal, and entorhinal cortices in the rat) constitutes the primary intermediary between the hippocampus and the neocortex and has been shown to participate critically in the temporary storage and ultimate consolidation of certain forms of memory thought to be dependent upon hippocampal processing (reviewed in [11]). Specifically, accumulating neuropsychological evidence suggests that damage of one or more of these cortical areas often results in profound memory impairment in both rats [18–20,32,37,38,43,52] and primates [2,31,49,57,58]. Furthermore, several recent reports have demonstrated learning-related alterations in the firing patterns of single cells within the rhinal cortices in both rats and primates [6,13,26,42,48,54,55]. Collectively these data suggest that the rhinal cortices may participate actively in the encoding of at least some forms of memory, and are generally consistent with the notion that interactions between these cortical areas and the hippocampus likely play a particularly prominent role in memory consolidation [11,44,56].

Attempts to characterize electrophysiologically the precise role of the hippocampus and rhinal cortices in memory have typically focused on an examination of the behaviorally-relevant firing properties of single cells within these areas during learning. With respect to the hippocampus, CA1 pyramidal cells have been reported to fire in either single action potentials or in high-frequency 'complex spike' discharges [41], both of which are typically phase-locked to the positive peak of ongoing dentate theta [51] (4–7 Hz) field activity [15,16,36]. Regarding the

* Corresponding author.

behavioral correlates of hippocampal unit activity, the most widely reported observation is that of 'place cells' that fire preferentially and robustly when the animal occupies a specific spatial location defined by its relation to extant environmental (e.g. visual, auditory, and olfactory) cues [29,30,33,34]. However, CA1 cells also exhibit robust behavioral correlates in a variety of explicitly non-spatial tasks, including delayed nonmatching to sample [35] and simultaneous odor discrimination [53]. In one study examining CA1 unit activity in rats engaged in either simultaneous odor discrimination learning or spatial learning [36], CA1 cells were observed to fire in complex spikes that were tightly phase-locked to the ongoing hippocampal theta rhythm. Moreover, during performance of both tasks, these bursts were typically preceded by either single action potentials or complex spikes at intervals corresponding to the theta rhythm (140–200 ms), suggesting that these cells were discharging repetitively at the theta frequency. Importantly, during the simultaneous odor discrimination task, this 'theta-bursting' pattern emerged most frequently during behavioral events associated with likely periods of mnemonic processing, including periods of stimulus sampling and response generation.

An examination of the potential relationship between behaviorally-relevant patterns of hippocampal unit activity and alterations of synaptic efficacy in the hippocampus [24] has revealed that stimulation of Schaffer commissural/collateral (SC) fibers preferentially induces long-term potentiation (LTP) in CA1 when delivered in a pattern that mimics the learning-related theta-bursting firing repertoire of CA1 pyramidal cells described above. That is, LTP in this pathway is preferentially induced by repetitive high frequency bursts of stimulation (i.e., 4 or 5 pulses at 100 Hz, mimicking a complex spike discharge) delivered at the theta frequency (5 to 10 Hz); this pattern is typically referred to 'theta-burst' stimulation (TBS) [1,23]. Moreover, LTP in the hippocampus can be induced by a single burst if preceded by another burst [23] or single pulse [10] at a latency which corresponds to the theta interval. Further, TBS is most effective in inducing LTP in the dentate gyrus when delivered in phase with local theta rhythm [39]. When considered together with the data described above, these findings suggest that the neurophysiological conditions appropriate for the naturally-occurring enhancement of synaptic efficacy in the hippocampus often accompany mnemonically-relevant behavioral events.

Although hippocampal LTP has been shown to last for several weeks in chronic recording preparations [46], its expression in vitro is sensitive to anoxia induced within a brief (2 min) vulnerable period following tetanization [1]. Moreover, when delivered within minutes of potentiation, trains of single-pulse stimulation (1–10 Hz) delivered to SC fibers result in a long-lasting reversal, or depotentiation, of LTP in CA1 both in vitro [25,45] and in vivo ([3,47]; but see [12]). Unlike hippocampal homosynaptic long-term depression (LTD) [4,17,28,50], depotentiation is dependent upon prior synaptic enhancement, and is preferentially induced by single pulse stimulation delivered at latencies which parallel theta (5–10 Hz 'theta-pulse' stimulation; TPS) [25,47]. Together with the data regarding theta-bursting patterns of hippocampal activation described above, these data suggest that theta-related hippocampal unit activity may play an important role not only in the induction of activity-dependent synaptic enhancement within the hippocampus, but also in its reversal.

Collectively, the findings described above suggest that distinctly different patterns of theta-related hippocampal stimulation (TBS and TPS) modeled after behaviorally-relevant patterns of CA1 unit activity (bursts and single spikes, respectively) result in the induction and reversal of activity-dependent synaptic plasticity within the hippocampus. Given that certain forms of memory appear to depend critically on interactions between the hippocampus and rhinal cortical areas, that these areas share dense monosynaptic and reciprocal interconnections, and that examination of LTP in the CA1–rhinal cortex pathway represents a logical extension of the study of LTP within the hippocampal system, the aim of the present study was to determine whether TBS and TPS delivered to CA1 would reliably alter synaptic efficacy within the rhinal cortical targets of the hippocampus.

2. Materials and methods

2.1. Subjects

Twelve male Sprague–Dawley rats (Harlan, Indianapolis, IN; 300–450 g) served as Ss. Several Ss served as controls in an unrelated behavioral experiment; while they had previously been food deprived, none received pharmacological or neuropsychological manipulations. All Ss were maintained individually in suspended wire mesh cages on a 12:12 h light:dark schedule and received both food and water ad libitum for at least three days prior to preparation for electrophysiological procedures. During this period Ss were handled for at least 5 min each day. All electrophysiological procedures were conducted during the light phase of the cycle.

2.2. Surgical procedures

Ss were anesthetized with urethane (3 mg/kg, ip; Sigma, St. Louis, MO) supplemented with a low dose of sodium pentobarbital (10 mg/kg, ip; Sigma) and were mounted in a standard stereotaxic frame (Activational Systems, Warren, MI). The cranium was exposed, and portions of the left parietal bone and dura overlying the areas of interest were removed.

A bipolar stimulating electrode consisting of twisted strands of Teflon-coated stainless steel wire (127 μm bare diameter; tips separated by approximately 1 mm) was

positioned within the CA1 pyramidal cell layer in the left mid-septotemporal hippocampus (AP: bregma −6.3 mm; ML: 5.5 mm; DV: −5.4 mm below dura). A monopolar recording electrode constructed from the same wire was positioned close to the border of the ipsilateral perirhinal and postrhinal cortices (PRh) [7] immediately dorsal to the rhinal fissure (AP: bregma −5.2 mm; ML: 4.3 mm; DV: −5.5 mm below dura at an angle of 17 degrees in the ML plane).

2.3. Electrophysiological procedures

During surgical positioning of the electrodes, single test pulses (150 μs width, 325 mA) were delivered to CA1 every 7.5 s. Evoked responses were amplified 1000× (10 Hz–5 kHz bandwidth; A–M Systems, Everitt, WA; model 1700) and passed in parallel to a digital storage oscilloscope and a microcomputer, where they were digitized at 10 kHz for subsequent analysis. The dorso-ventral position of the recording and, if necessary, stimulating electrode was adjusted slightly so as to maximize the PRh field potential. Stimulating current was then gradually increased to determine the maximum EPSP amplitude, and was subsequently reduced to a level sufficient to evoke an EPSP approximately one-half of its maximum amplitude. This reduced stimulation intensity was then used during recording of both baseline and potentiated responses.

Prior to the baseline recording period, two separate paired-pulse stimulation protocols were employed. First, paired pulses were delivered at 100 Hz (i.e., 10 ms interstimulus interval [ISI]) in order to determine whether the PRh EPSP was monosynaptically activated. Second, pulse pairs were delivered at 8.7 Hz (i.e., 115 ms ISI) in order to determine whether the CA1–PRh pathway exhibited paired-pulse facilitation, a form of short-term synaptic plasticity typically associated with enhanced pre-synaptic transmitter release. When more than one pulse pair was delivered, successive pulse pairs were separated by 7.5 s.

A 15 min baseline data collection period began approximately 10 min after the paired-pulse procedures were completed. During this baseline period, and for the remainder of each experiment (with the exception of periods of TBS or TPS), single pulse stimuli were delivered at 15 s intervals, and responses were saved to disk for subsequent analysis. Following this baseline period, TBS (2 bouts of 11 bursts [5 pulses at 100 Hz] with 140 ms between bursts [7 Hz] and 3 s between bouts; 110 pulses total) was delivered to CA1 at twice the baseline stimulation intensity; following TBS the stimulation intensity was returned to the basal level and single-pulse stimulation (15 s ISI) was resumed. In one group of preparations ($n = 8$), test pulse stimulation continued in an uninterrupted fashion for either 30 min ($n = 6$) or 60 min ($n = 2$). In a second group of preparations ($n = 4$), TPS (5 Hz, 1 min; 300 pulses total) was delivered at twice the baseline intensity 5 min after the delivery of TBS; test pulse stimulation was then resumed at the baseline intensity for a minimum of 24 min.

2.4. Histological verification of electrode placement

Following data collection, electrolytic lesions were produced at the electrode tips by passing anodal current (0.1 mA; 8–15 s) through both the stimulating and recording electrodes. Ss were then deeply anesthetized with sodium pentobarbital (100 mg/kg) and brains were extracted and stored in a 50% formalin–30% sucrose solution for at least 24 h. Brains were then frozen, sectioned coronally at 50 μm, and mounted on gelatin-subbed slides. Sections were stained either with natural red (0.2% solution) after exposure to a potassium ferrocyanide solution or with cresyl violet (0.1% solution). Electrode placement was verified with the aid of light microscopy.

3. Results

3.1. Localization of stimulating and recording electrodes

A summary of the electrode placements for all 12 preparations are presented in Fig. 1. All stimulating electrodes were positioned the CA1 pyramidal cell layer, and recording electrodes were positioned within the superficial layers of either perirhinal or postrhinal cortex dorsal to the rhinal fissure and, in several cases, close to the border of temporal cortex area 3 (TE3).

3.2. Characteristics of EPSPs in PRh evoked by stimulation of CA1

Single pulse stimulation of CA1 evoked a small amplitude (mean maximum amplitude, −0.325 mV; range, −0.2 to −0.48 mV), short latency (mean peak latency, 7.5 ms; range 6 to 9 ms) EPSP in PRh. All responses followed 100 Hz paired pulse stimulation, suggesting that they were monosynaptically activated. When pulse pairs were delivered at 8.7 Hz (115 ms ISI), paired-pulse facilitation was consistently observed.

3.3. Theta-burst stimulation induces long-term potentiation in the CA1–PRh projection

TBS resulted in a significant potentiation of both the peak amplitude and the slope of the initial, descending component of the PRh EPSP; description of relevant analyses will be limited to those concerning slope measures. Examination of EPSPs during the first 2 min following TBS stimulation revealed a pronounced short-term posttetanic potentiation (PTP) of PRh EPSP slope of at least 250 percent of baseline levels in 3 of 12 preparations. In the remaining nine preparations, PTP was either ambiguous or absent. Neither differences in other response characteristics

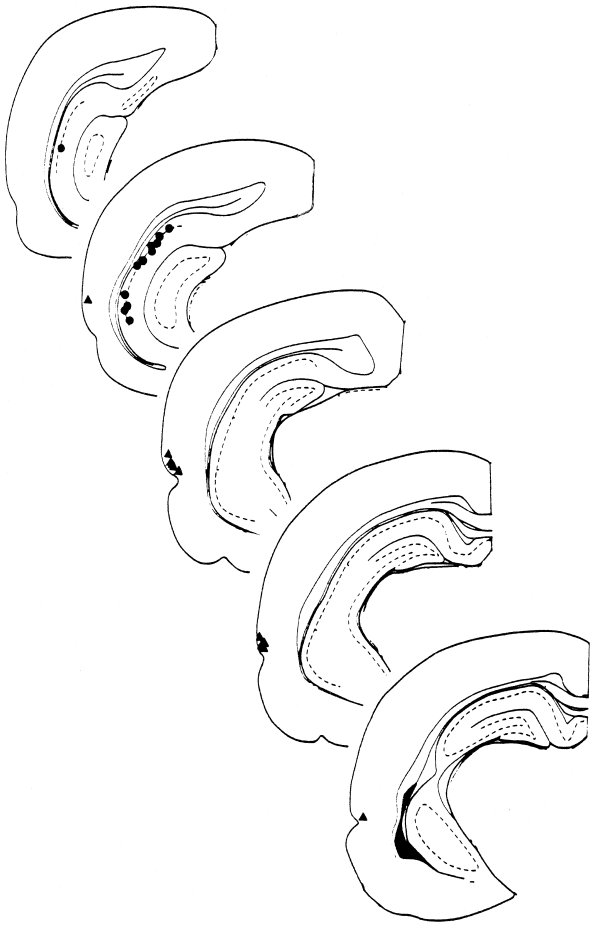

Fig. 1. Summary of stimulating (circles) and recording (triangles) electrode placement for all preparations. Stimulating electrodes were consistently placed within the CA1 pyramidal cell layer in the mid-septotemporal hippocampus and recording electrodes were consistently placed within the superficial layers of the perirhinal and postrhinal cortices, dorsal to the rhinal fissure.

nor systematic variation in electrode placement could readily account for the observed variability in PTP induction.

Stable LTP was induced in each of the eight preparations in which TBS was delivered alone. As illustrated in Fig. 2, no obvious alterations in peak latency were evident following TBS, and potentiation was long-lasting. EPSP slope remained, on average, 186% of baseline levels 30 min after TBS. A dependent samples *t*-test verified that EPSP slope during the last 2 min period of the recording session, Min 29–30, was significantly greater than that recorded during the 2 min period immediately preceding TBS ($t_7 = 10.94$; $p < 0.001$). As described above, responses were recorded for 60 min following TBS in 2 preparations; average EPSP slope for these preparations at Min 59–60 was 181.6% of baseline (data not shown).

3.4. Theta-pulse stimulation transiently suppresses long-term potentiation of the PRh EPSP

In the four preparations in which TPS was delivered 5 min after TBS, potentiation during the intervening 5 min period was comparable to that of the eight potentiated control preparations described above. EPSP slope during Min 4–5 after TBS was, on average, 217.4% and 237.1% of baseline for TPS preparations and potentiated control preparations, respectively; an independent samples *t*-test conducted on these data revealed no significant between group difference ($t_{10} = 0.61$; ns).

The effect of TPS on potentiated responses was assessed by examining post-TPS responses expressed as a percentage of potentiated response slope recorded during Min 4–5 after TBS. As illustrated in Fig. 3, EPSP slope was markedly attenuated during the first few minutes after TPS, followed by a gradual return to the level of the potentiated control preparations. In order to analyze statistically the observed recovery following TPS, a two-way repeated measures ANOVA was conducted to compare the data for potentiated control and TPS preparations at three separate 2 min periods following TBS: Min 7–8, 18–19, and 29–30 (see Table 1). This analysis revealed a highly significant Min by Condition interaction ($F_{2,35} = 3.58$; $p < 0.001$) but no significant main effect for either Min ($F_{2,35} = 1.30$; *ns*) or Condition ($F_{1,10} = 3.58$; *ns*). Subsequent post-hoc analyses (Student–Newman–Keuls) revealed that the percent potentiated slope for the TPS group

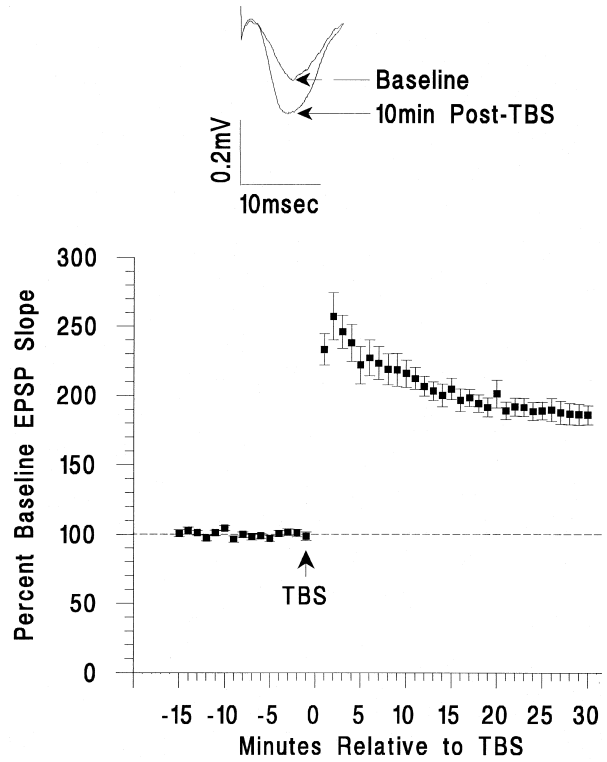

Fig. 2. Long-term potentiation in the perirhinal and postrhinal cortices induced by theta-burst stimulation (TBS). (Top) Representative EPSPs recorded immediately prior to and 10 min after TBS. Each response represents an average of four successive EPSPs recorded at 15 s intervals. Calibration: 0.2 mV, 10 ms. (Bottom) Mean EPSP slope for all preparations receiving TBS only ($n = 8$). Values represent slope averages (± 1 SEM) for four successive EPSPs recorded at 15 s intervals during each minute.

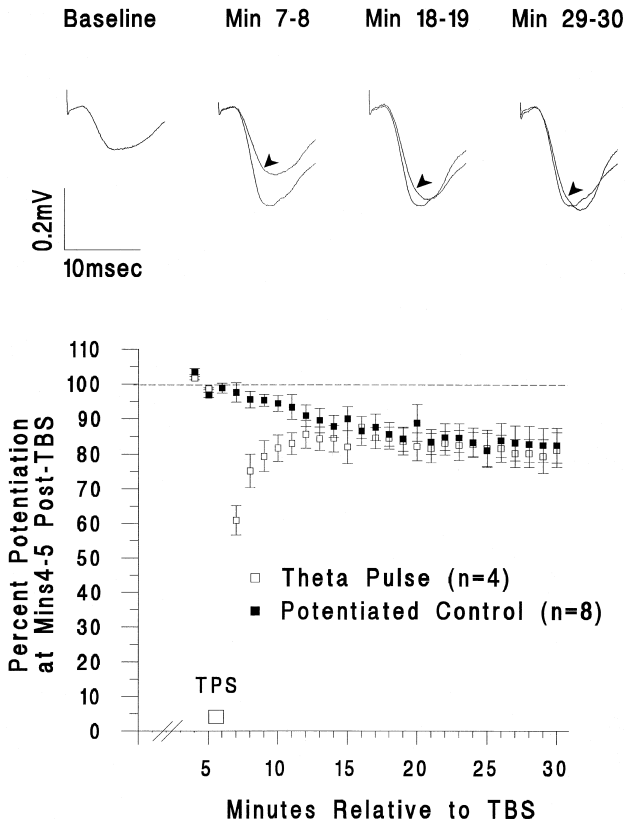

Fig. 3. Transient suppression of LTP induced in the perirhinal and postrhinal cortices by theta-pulse stimulation (TPS). (Top) Representative EPSPs recorded from TPS preparations during three separate 2 min periods following TBS (arrows), superimposed on the potentiated response recorded at Min 4–5 post-TBS. Calibration: 0.2 mV, 10 ms. (Bottom) Mean (±1 SEM) percent of potentiated EPSP slope recorded during Min 4–5 after TBS.

was significantly lower than that of the potentiated control group during Min 7–8 following TBS but not during either of the subsequent 2 min periods. Additional within-group post-hoc analyses (Student Newman Keuls) revealed that, for the TPS group, percent potentiated slope was significantly lower during Min 7–8 after TBS compared to each of the subsequent periods and that, for the potentiated control group, percent potentiated slope was significantly higher during Min 7–8 after TBS than at later periods. No other post-hoc comparisons reached significance.

Table 1
Minutes relative to TBS

Min	7–8	18–19	29–30
Potentiated control ($n = 8$)	92.81 (4.74)	84.95 (3.29)	82.43 (4.9)
Theta pulse ($n = 4$)	67.99 (4.29)	84.02 (3.5)	80.17 (4.77)

Mean percent potentiated EPSP slope for potentiated control and theta pulse Ss during three 2 min periods after potentiation. Values represent percentages of each subject's EPSP slope during Min 4–5 after TBS. Standard error of the mean is presented in parentheses.

4. Discussion

These data indicate that patterns of hippocampal stimulation that mimic the behaviorally-relevant, theta-modulated activity of CA1 pyramidal cells result in both short- and long-term alterations of synaptic efficacy within the rhinal cortical targets of CA1: TBS delivered to CA1 induced robust and long-lasting potentiation of PRh EPSP slope, while TPS delivered to CA1 5 min after TBS resulted in a substantial but transient suppression of EPSP slope.

As described previously, both perirhinal and postrhinal cortices receive direct ipsilateral projections from CA1 [8]; the present data suggest that this pathway is sufficiently dense and appropriately organized to evoke a substantial population EPSP in PRh. Despite these direct projections, however, it is possible that the present responses represented volume conducted field EPSPs generated in entorhinal cortex. Although depth profiles were not collected, it is likely that the responses recorded in PRh were locally generated since they typically both developed and dissipated rapidly as the recording electrode was advanced over short distances ventrally through PRh. Indeed, slight retraction of the recording electrode was often required in order to maximize response amplitude. The notion that the PRh responses were monosynaptically activated is suggested by the short EPSP peak latencies observed, which were roughly equivalent to orthodromic spike latencies in the monosynaptic projections to entorhinal cortex from both the subiculum and CA3 [14]. This conclusion is further supported by the finding that the present responses followed 100 Hz stimulation.

Although several recent studies have demonstrated intracortical LTP in vitro in rhinal cortical areas [5,9], the present data are the first to demonstrate that PRh can support LTP in vivo following activation of its hippocampal afferents. However, it is presently unclear whether activation of the hippocampus using stimulation protocols other than TBS would induce LTP within PRh. TBS most appropriately mimics endogenous, behaviorally-relevant patterns of hippocampal unit activity [23,24,36] and has been shown to induce LTP in CA1 more robustly by TBS than by bursting stimulation delivered at intervals outside the theta range [24]. However, Laroche and colleagues [22] have demonstrated that LTP can be induced in the hippocampal projection to the prelimbic area of prefrontal cortex [21] following high-frequency tetanic stimulation (400 Hz) of CA1, suggesting that TBS may be only one of several high-frequency stimulation patterns effective in inducing LTP in cortical targets of the hippocampus. The efficacy of TBS in inducing intra-hippocampal LTP is apparently related to the correspondence between the theta interval and the time course of maximal $GABA_B$-mediated disinhibition, which likely enhances NMDA receptor-mediated calcium currents [27]. Whether similar mechanisms are invoked during the induction of LTP in the

CA1–PRh pathway is at present unclear. Thus, although a determination of both the optimal stimulation parameters and the physiological mechanisms underlying the induction of LTP in the CA1–PRh pathway await further study, the present data indicate that TBS results in a robust and lasting potentiation in PRh.

Racine and coworkers have suggested that neocortical LTP is difficult to induce, requiring repeated daily exposures to conditioning trains [40]. The present data are generally consistent with the notion that fundamental differences in the characteristics of synaptic plasticity exist between the hippocampus and the neocortex. Single pulse stimulation is most effective in producing a long-lasting reversal of LTP in CA1 when delivered at theta frequency [25,47] soon after potentiation, with maximal depotentiation at latencies of 1 to 6 min following LTP induction [45]. In the present study, a stimulation protocol identical to that previously shown to produce a long-lasting depotentiation in the hippocampus in vivo [47] resulted in only a transient suppression of LTP in PRh. This pattern of results could possibly indicate variation between the hippocampus and its cortical targets in the maintenance characteristics of LTP. Whether TPS delivered to CA1 would result in short- or long-term forms of homosynaptic depression in PRh that are independent of prior synaptic enhancement remains to be determined.

In conclusion, the present findings demonstrate that theta-related patterns of hippocampal activation can induce bidirectional modifications of synaptic efficacy within the perirhinal and postrhinal cortices. Further, the present findings are consistent with the notion that one function of the hippocampal theta rhythm may be to modulate endogenous patterns of hippocampal unit activity during mnemonically-relevant behavioral periods, perhaps resulting in a naturally-occurring alteration of synaptic efficacy within its rhinal cortical targets.

Acknowledgements

This study was supported by NSF grant IBN9514526 and a grant from the Charles and Joanna Busch Biomedical Research Fund. The authors would like to thank Brian Grossman for assistance with data collection and analysis.

References

[1] A. Arai, J. Larson, G. Lynch, Anoxia reveals a vulnerable period in the development of long-term potentiation, Brain Res. 511 (1990) 353–357.
[2] P. Alvarez-Royo, S. Zola-Morgan, L.R. Squire, Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys, J. Neurosci. 15 (5 pt. 2) (1995) 3798–3807.
[3] G. Barrionuevo, F. Schottler, G. Lynch, The effects of repetitive low frequency stimulation on control and 'potentiate' responses in the hippocampus, Life Sci. 27 (1980) 2385–2391.
[4] M.F. Bear, R.C. Malenka, Synaptic plasticity: LTP and LTD, Curr. Opin. Neurobiol. 4 (1993) 389–399.
[5] D.K. Bilkey, Long-term potentiation in the in vitro perirhinal cortex displays associative processes, Brain Res. 733 (1996) 297–300.
[6] M.W. Brown, F.A.W. Wilson, I.P. Riches, Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory, Brain Res. 409 (1987) 158–162.
[7] R.D. Burwell, M.P. Witter, D.G. Amaral, Perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain, Hippocampus 5 (1995) 390–408.
[8] T.W. Deacon, H. Eichenbaum, P. Rosenberg, K.W. Eckmann, Afferent connections of the perirhinal cortex in the rat, J. Comp. Neurol. 220 (1983) 168–190.
[9] M. deCurtis, R.R. Llinas, Entorhinal cortex long-term potentiation evoked by theta-patterned stimulation of associative fibers in the isolated in vitro guinea pig brain, Brain Res. 600 (1993) 327–330.
[10] D. Diamond, T. Dunwiddie, G. Rose, Characteristics of hippocampal primed burst potentiation in vitro and in the awake rat, J. Neurosci. 8 (1988) 4079–4088.
[11] H. Eichenbaum, T. Otto, N.J. Cohen, Two functional components of the hippocampal memory system, Behav. Brain Sci. 17 (1994) 449–517.
[12] M.L. Errington, T.V.P. Bliss, G. Richter-Levin, K. Yenk, S. Laroche, Stimulation at 1–5 Hz does not produce long-term depression of depotentiation in the hippocampus of the adult rat in vivo, J. Neurophysiol. 74 (1995) 1793–1799.
[13] F.L. Fahy, I.P. Riches, M.W. Brown, Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex, Exp. Brain Res. 96 (1993) 457–472.
[14] D.M. Finch, E.E. Wong, E.L. Derian, T.L. Babb, Neurophysiology of limbic system pathways in the rat: Projections from the subicular complex and hippocampus to the entorhinal cortex, Brain Res. 397 (1986) 205–213.
[15] S.E. Fox, J.B. Ranck Jr., Electrophysiological characteristics of hippocampal complex-spike cells and theta cells, Exp. Brain Res. 41 (1981) 399–410.
[16] S.E. Fox, S. Wolfson, J.B. Ranck Jr., Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats, Exp. Brain Res. 62 (1986) 495–508.
[17] A.J. Heynen, M.F. Bear, A.C. Abraham, Low-frequency stimulation induces homosynaptic LTD in the CA1 region of the adult rat hippocampus in vivo, Soc. Neurosci. Abstr. 21 (1995) 2005.
[18] C. Herzog, T. Otto, Odor-guided fear conditioning. II. Lesions of the anterior perirhinal cortex disrupt fear conditioning to the explicit CS but no the training context, Behav. Neurosci., in press.
[19] M.E. Hunt, R.P. Kesner, R.B. Evans, Memory for spatial location: Functional dissociation of entorhinal cortex and hippocampus, Psychobiology 22 (3) (1994) 186–194.
[20] L.E. Jarrard, H. Okaichi, O. Steward, R.B. Goldschmidt, On the role of hippocampal connections in the performance of place and cue tasks: Comparisons with damage to hippocampus, Behav. Neurosci. 98 (6) (1984) 946–954.
[21] T.M. Jay, J. Glowinski, A.M. Thierry, Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat, Brain Res. 505 (1989) 337–340.
[22] S. Laroche, T.M. Jay, A. Theirry, Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region, Neurosci. Lett. 114 (1990) 184–190.
[23] J. Larson, G. Lynch, Induction of synaptic potentiation in the hippocampus involves two events, Science 232 (1986) 985–988.
[24] J. Larson, D. Wong, G. Lynch, Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation, Brain Res. 368 (1986) 347–350.

[25] J. Larson, P. Xiao, G. Lynch, Reversal of LTP by theta-frequency stimulation, Brain Res. 600 (1993) 97–102.
[26] L. Li, E.K. Miller, R. Desimone, The representation of stimulus familiarity in anterior inferior temporal cortex, J. Neurophysiol. 69 (1993) 1918–1929.
[27] D.D. Mott, D.V. Lewis, Facilitation of the induction of long-term potentiation by $GABA_B$ receptors, Science 252 (1991) 1718–1720.
[28] R.M. Mulkey, R.C. Malenka, Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus, Neuron 9 (1992) 967–975.
[29] R.U. Muller, J.L. Kubie, The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells, J. Neurosci. 7 (7) (1987) 1951–1968.
[30] R.U. Muller, J.L. Kubie, J.B. Ranck Jr., Spatial firing patterns of hippocampal complex-spike cells in a fixed environment, J. Neurosci. 7 (7) (1987) 1935–1950.
[31] E.A. Murray, Medial temporal lobe structures contributing to recognition memory. The amygdaloid complex versus the rhinal cortex, in: J.P. Aggleton (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, Wiley, New York, pp. 453–470.
[32] T. Myhrer, K. Wangen, Marked retrograde and anterograde amnesia of a visual discrimination task in rats with selective lesions or the perirhinal cortex, Neurobiol. Learn. Mem. 65 (1996) 244–252.
[33] J. O'Keefe, Place units in the hippocampus of the freely moving rat, Exp. Neurol. 51 (1976) 78–109.
[34] J. O'Keefe, J. Dostrovsky, The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely moving rat, Brain Res. 34 (1971) 171–175.
[35] T. Otto, H. Eichenbaum, Neuronal activity in the hippocampus during delayed non-match to sample performance in rats: Evidence for hippocampal processing in recognition memory, Hippocampus 2 (3) (1992) 323–334.
[36] T. Otto, H. Eichenbaum, S.I. Weiner, C.G. Wible, Learning-related patterns of CA1 spike trains parallel stimulation parameters optimal for inducing hippocampal long-term potentiation, Hippocampus 1 (1991) 181–192.
[37] T. Otto, D. Wolf, T.J. Walsh, Combined lesions of the perirhinal and entorhinal cortex impair rats' performance in two versions of the spatially-guided radial arm maze, Neurobiol. Learn. Mem., in press.
[38] T. Otto, D. Garruto, Rhinal cortical lesions impair simultaneous olfactory discrimination learning in rats, Behav. Neurosci., in press.
[39] C. Pavlides, Y.I. Greenstein, M. Grudman, J. Winson, Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of the theta rhythm, Brain Res. 439 (1988) 383–387.
[40] R.J. Racine, C.A. Chapman, C. Trepel, G.C. Teskey, N.W. Milgram, Post-activation potentiation in the neocortex IV. Multiple sessions required for induction of long-term potentiation in the chronic preparation, Brain Res. 702 (1995) 87–93.
[41] J.B. Ranck Jr., Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats Part I. Behavioral correlates and firing repertoires, Exp. Neurol. 41 (1973) 461–531.
[42] I.P. Riches, F.A.W. Wilson, M.W. Brown, The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate, J. Neurosci. 11 (6) (1991) 1763–1779.
[43] J.B. Rosen, J.M. Hitchcock, M.J.D. Miserendino, W.A. Falls, S. Campeau, M. Davis, Lesions of the perirhinal cortex but not of the frontal, medial prefrontal, visual, or insular cortex block fear-potentiated startle using a visual conditioned stimulus, J. Neurosci. 12 (12) (1992) 4624–4633.
[44] L.R. Squire, Memory and Brain, Oxford Univ. Press., New York, 1987.
[45] U. Staubli, D. Chun, Factors regulating the reversibility of long-term potentiation, J. Neurosci. 16 (1996) 853–860.
[46] U. Staubli, G. Lynch, Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation, Brain Res. 435 (1987) 227–234.
[47] U. Staubli, G. Lynch, Stable depression of potentiated synaptic responses in the hippocampus with 1–5 Hz stimulation, Brain Res. 513 (1990) 113–118.
[48] W.A. Suzuki, E.K. Miller, R. Desimone, Object and place memory in the macaque entorhinal cortex, J. Neurophysiol., in press.
[49] W.A. Suzuki, S. Zola-Morgan, L.R. Squire, D.G. Amaral, Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities, J. Neurosci. 13 (1993) 2430–2451.
[50] E. Thiels, G. Barrionuevo, T.W. Berger, Excitatory stimulation during postsynaptic inhibition induces long-term depression in hippocampus in vivo, J. Neurophysiol. 72 (1994) 3009–3116.
[51] C. Vanderwolf, Hippocampal electrical activity and voluntary movement in the rat, Electroenceph. Clin. Neurophysiol. 26 (1969) 407–418.
[52] K.A. Wiig, D.K. Bilkey, Perirhinal cortex lesions in rats disrupt performance in a spatial DNMS task, NeuroReport 5 (1994) 1405–1408.
[53] S.I. Weiner, C.A. Paul, H. Eichenbaum, Spatial and behavioral correlates of hippocampal neuronal activity, J. Neurosci. 9 (8) (1989) 2737–2763.
[54] B.J. Young, T. Otto, G.D. Fox, H. Eichenbaum, Memory representation within the parahippocampal region, J. Neurosci., in press.
[55] X.O. Zhu, M.W. Brown, J.P. Aggleton, Neuronal signaling of information to visual recognition memory in rat rhinal and neighboring cortices, Eur. J. Neurosci. 7 (1995) 753–765.
[56] S. Zola-Morgan, L.R. Squire, P. Alvarez-Royo, R.P. Clower, Independence of memory functions and emotional behavior: Separate contributions of the hippocampal formation and the amygdala, Hippocampus 1 (2) (1991) 207–220.
[57] S. Zola-Morgan, L.R. Squire, D.G. Amaral, W.A. Suzuki, Lesions of perirhinal and parahippocampal cortex that spare amygdala and hippocampal formation produce severe memory impairment following lesion of the hippocampal formation, J. Neurosci. 9 (1989) 4355–4370.
[58] S. Zola-Morgan, L.R. Squire, R.P. Clower, N.L. Rempel, Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation, J. Neurosci. 13 (1993) 251–265.