Associative Synaptic Plasticity in Hippocampal CA1 Neurons Is Not Sensitive to Unpaired Presynaptic Activity

DEAN V. BUONOMANO AND MICHAEL M. MERZENICH
Keck Center for Integrative Neuroscience, University of California, San Francisco, California 94143

SUMMARY AND CONCLUSIONS

1. Hebbian or associative synaptic plasticity has been proposed to play an important role in learning and memory. Whereas many behaviorally relevant stimuli are time-varying, most experimental and theoretical work on synaptic plasticity has focused on stimuli or induction protocols without temporal structure. Recent theoretical studies have suggested that associative plasticity sensitive to only the conjunction of pre- and postsynaptic activity is not an effective learning rule for networks required to learn time-varying stimuli. Our goal in the current experiment was to determine whether associative long-term potentiation (LTP) is sensitive to temporal structure. We examined whether the presentation of unpaired presynaptic pulses in addition to paired pre- and postsynaptic activity altered the induction of associative LTP.

2. By using intracellular recordings from CA1 pyramidal cells, associative long-term potentiation (LTP) was induced in a control pathway by pairing a single presynaptic pulse with postsynaptic depolarization every 5 s (50–70×). The experimental pathway received the same training, with additional unpaired presynaptic pulses delivered in close temporal proximity, either after or before associative pairing. Five separate sets of experiments were performed with intervals of −200, −50, +50, +200, or +800 ms. Negative intervals indicate that the unpaired presynaptic pulse was presented before the depolarizing pulse. Our results showed that the presence of unpaired presynaptic pulses, occurring either before or after pairing, did not significantly alter the magnitude of LTP.

3. The experimental design permitted an analysis of whether changes in paired-pulse facilitation (PPF) occur as a result of associative LTP. The average degree of PPF was the same before and after LTP. However, there was a significant inverse correlation between the initial degree of PPF and the degree of PPF after LTP. There was no relationship between the change in PPF, and whether the first or second pulse had been paired with depolarization.

4. These results indicate that the presence of unpaired presynaptic pulses does not alter the induction of synaptic plasticity, suggesting that plasticity of the Schaffer collateral-CA1 synapse is primarily conjunctive rather than correlative.

INTRODUCTION

Hebbian or associative synaptic plasticity is regarded as one of the principal neural mechanisms underlying learning and memory. Indeed, theoretical work has shown that Hebbian plasticity, like that described in CA1 pyramidal cells and neocortex (Kelso et al. 1986; Kirkwood et al. 1993; Kirkwood and Bear 1994; Sastry et al. 1986; Wigström et al. 1986), is a powerful learning rule. For example, when incorporated into artificial neural networks, Hebbian plasticity can account for the development of stimulus-specific neuronal responses and the formation of topographic maps (Grajski and Merzenich 1990; Miller et al. 1989; Pearson et. al. 1987; Ritter and Kohonen 1989; von der Malsburg 1973).

To date, most theoretical studies that have used Hebbian plasticity have dealt with the representation of spatial, or nontime-varying stimuli, i.e., stimuli characterized by the spatial patterns of activity produced at the sensory layers. Stimuli that do not vary in time, such as a tone, a bar of light, or a picture of a face represent only a portion of the repertoire of such naturally occurring stimuli. Many behaviorally relevant stimuli are time-varying. In speech, music, and motion processing, the sequence and duration of events as well as the interval between events are important. It is not immediately clear whether Hebbian plasticity is an effective learning rule for the representation of time-varying stimuli. Indeed, recent theoretical work has shown that the incorporation of Hebbian plasticity into a network capable of solving temporal tasks can degrade the representation of time-varying stimuli (Buonomano and Merzenich 1995; see DISCUSSION).

One reason the role of Hebbian plasticity in temporal information processing is not well understood is that relatively little experimental data has addressed how temporal structure affects the induction of associative synaptic plasticity. For example, given that many naturally occurring stimuli are time-varying and may last a few hundred milliseconds it may be expected that during stimulus presentation synapses experience periods of both paired and unpaired activity. However it is not clear whether unpaired activity in close temporal proximity to paired pre- and postsynaptic activity effects the induction of associative long-term potentiation (LTP). From a computational point of view, if associative LTP is indeed sensitive to correlations, one might expect that synapses that experience both paired and unpaired pre- and postsynaptic activity might exhibit less facilitation then synapses subject only to paired activity.

Our goal in the current experiments was to determine whether associative LTP induced by pairing was affected by the presence of unpaired presynaptic pulses presented in close temporal proximity to paired pre- and postsynaptic activity. By presenting unpaired pulses at five different intervals both before and after pairing we showed that associative LTP was unaffected by the presence of unpaired presynaptic activity. We also examined whether or not there were any changes in paired-pulse facilitation(PPF) as a result of associative LTP. Although there were no changes in the average degree of PPF, in agreement with the results of Schulz et al. (1994), there was an inverse correlation between the degree of PPF before versus that after the induction of LTP.
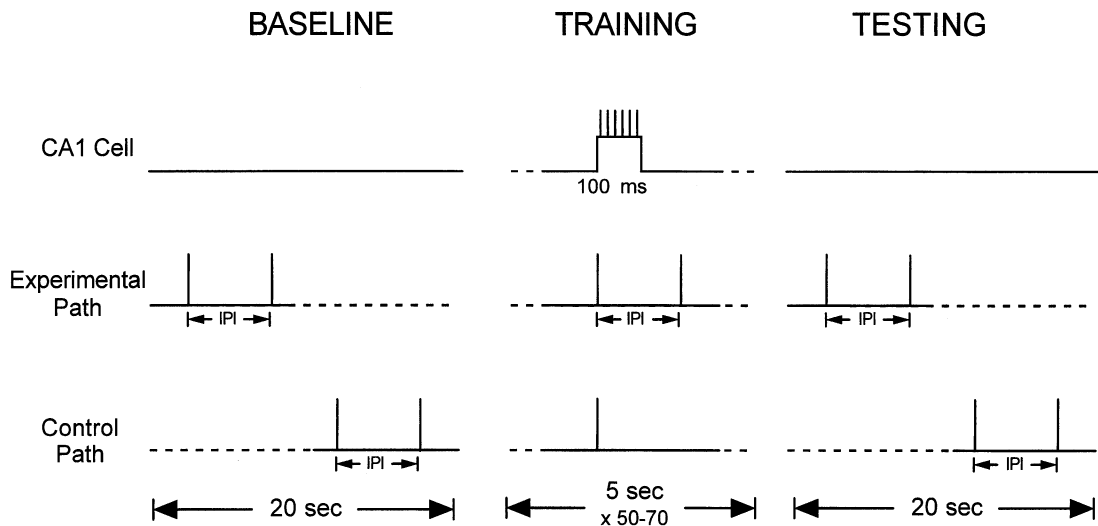
BASELINE   TRAINING   TESTING

FIG. 1. Experimental protocol. Intracellular recordings were made from CA1 cells while stimulating 2 independent pathways. Each pathway received either single or paired pulses during the baseline and testing phases. During training, the control pathway received a single pulse paired with a 100-ms depolarizing step to the postsynaptic cell. Pairing occurred every 5 s for a total of 50–70 times. Experimental pathway was also activated in conjunction with the depolarizing step, but in addition received an unpaired pulse at 1 of 5 different interpulse intervals (IPI). Interpulse intervals used were −200, −50, +50, +200, and +800 ms.

MATERIALS AND METHODS

Preparation

Experiments were performed on 400-μm thick transverse hippocampal slices from Sprague-Dawley rats (21–40 days). The hippocampus was removed after anesthesia with pentobarbital sodium and decapitation. Slices were cut and submerged in a oxygenated medium comprised of the following (in mM): 119 NaCl, 2.5 KCl, 1.3 $MgSO_4$, 1.0 NaH_2PO_4, 26.2 $NaCO_3$, 2.5 $CaCl_2$, and 10 glucose. After an equilibrium period of at least 1 h, slices were transferred to a recording chamber perfused at a rate of 2 ml/min and maintained at a temperature of 30–31°C.

Recording and stimulation

Intracellular recordings from CA1 pyramidal neurons were made with 40–100 MΩ electrodes filled with 3-M KAc. Two stainless steel bipolar electrodes were used for stimulation (0.1 ms, 5 - 30 μA). Stimulating electrodes were placed in the stratum radiatum, near the CA3-CA1 border, and at the subicular end of CA1. Cell penetrations were considered acceptable if the resting potential was below −60 mV, the input resistance was ≥30 MΩ, and there were overshooting action potentials. The two pathways were considered independent if there was no PPF when both pathways were stimulated 50-ms apart. At the end of experiments, pathway independence was also confirmed by observing no changes in EPSP amplitude in one pathway as a result of a tetanic stimulus applied in the second pathway.

The training protocol is schematized in Fig. 1. Pathways were randomly assigned as experimental or control. During Baseline and Testing, EPSPs were elicited with paired pulses (in some experiments single pulses were used). Training was begun after recording stable EPSPs for at least 10 min; single pulses were elicited in both pathways and paired with a 100-ms depolarizing pulse (2–4 nA). The experimental pathway received an additional pulse at one of five different interpulse intervals: −200, −50, +50, +200, +800 (an interval of −200 ms indicates that the unpaired pulse preceded the paired pulse by 200 ms). Training consisted of 50 to 70 pairings presented every 5 s. The inclusion of the +50 ms interval, in which both pulses were paired with postsynaptic

depolarization, was to determine whether pairing two pulses produced a significant enhancement of LTP.

Data analysis

The experiment was designed to assess differences in the degree of associative LTP between the control and experimental pathways. Only experiments in which at least one pathway exhibited LTP (more than a 20% increase in excitatory postsynaptic potential (EPSP) amplitude 30-min after training) are included here. Both EPSP amplitude and slope were used as measures of synaptic plasticity; both yielded similar results. Unless otherwise noted amplitude measures are presented. For average data and statistical analyses LTP was defined as the average facilitation 27–32 min after training. Two-tailed paired t-tests were used to examine the differences in facilitation between the experimental and control pathways. Percent PPF was defined as the ratio of the amplitude of second and first EPSP multiplied by 100.

RESULTS

In both the experimental and control pathway, single pulses were paired with a 100-ms depolarizing pulse during training. In the experimental pathway, additional unpaired presynaptic pulses were presented at one of five different intervals: −200, −50, +50, +200, and +800. Figure 2 displays a representative example of a single experiment with an interpulse interval of +200 ms. During training both pathways were simultaneously paired with the onset of a 100-ms depolarizing pulse, while the experimental pathway received an additional pulse at 200 ms, as indicated by the EPSP that occurred after the end of the depolarizing pulse. The degree of facilitation in both the control and experimental pathway was approximately 60%.

Average data for each group revealed no significant differences between the experimental and control pathways. Figure 3 shows the average degree of facilitation in both the experimental and control pathways 30 min after training for
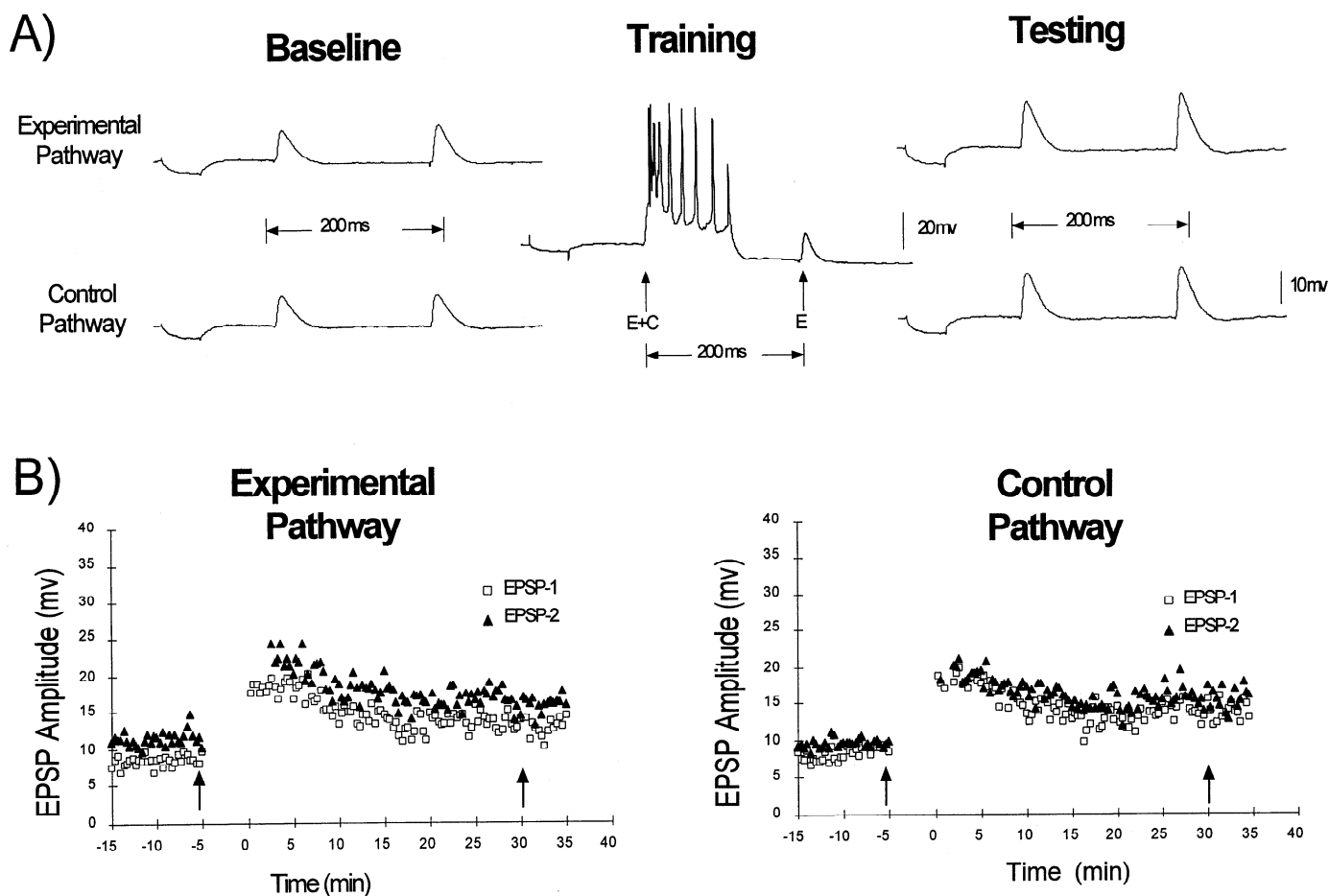
FIG. 2. Representative experiment using a +200-ms interpulse interval. A: excitatory postsynaptic potentials (EPSPs) produced by both pathways at different phases of the experiment. During training, both the experimental and control paths (E + C) were stimulated in conjunction with the depolarizing pulse. Experimental pathway received an additional unpaired pulse (E) 200-ms after the onset of the depolarizing step. B: degree of LTP was similar in both the experimental and control path. EPSP-1 and EPSP-2 represent the amplitude of the EPSP produced by the 1st and 2nd pulse to each pathway. ↑, time points from which the baseline and testing traces in A were obtained.

all five intervals. For all intervals examined there was no significant difference between the control and experimental pathways. In particular there was no tendency for decreased LTP for all intervals examined, despite the presence of unpaired pulses. There was a trend ($P < 0.1$) for increased LTP in the experimental pathway for the +50-ms group, in which both pulses were paired with the postsynaptic activity. However, the lack of a significant enhancement suggests that the presence of a second pulse paired with postsynaptic activity does not further enhance the induction of associative LTP over multiple trials.

Changes in paired-pulse facilitation

The experimental design also permitted an analysis of whether the magnitude of PPF changes as a result of associative LTP. For this analysis, the experimental and control data from the −200, −50, +50, +200 group were used. As expected, PPF was more pronounced in the 50-ms groups than in the 200-ms groups. However because the effects of LTP on PPF were the same for both intervals, the data was pooled for the correlation analysis. The +800-ms group was not used because at this interval there was no significant PPF.

On average there was no significant change in the magnitude of PPF after the induction of LTP. PPF before LTP was $140 \pm 3\%$ (mean $\pm$SE; $139 \pm 4\%$, for EPSP slope). After the induction of LTP, average PPF was $138 \pm 3\%$ ($138 \pm 3\%$, slope). Although there was no change in PPF when all cells were averaged, there was an inverse correlation between the degree of PPF before and after LTP (Fig. 4). The correlation between initial PPF and PPF after LTP was $r = -0.544$, $P < 0.0004$, $n = 36$ ($r = -0.62$, $P < 0.0001$, slope). LTP tended to decrease PPF if the initial PPF was above 35%, and increase it if initial PPF was below 35%.

DISCUSSION

Associative plasticity and temporal structure

Hebbian or associative synaptic plasticity is regarded as one of the principal neural mechanisms underlying learning and memory. Although a large number of experimental studies have examined synaptic plasticity, relatively little is known the sensitivity of plasticity to the temporal structure of inputs.
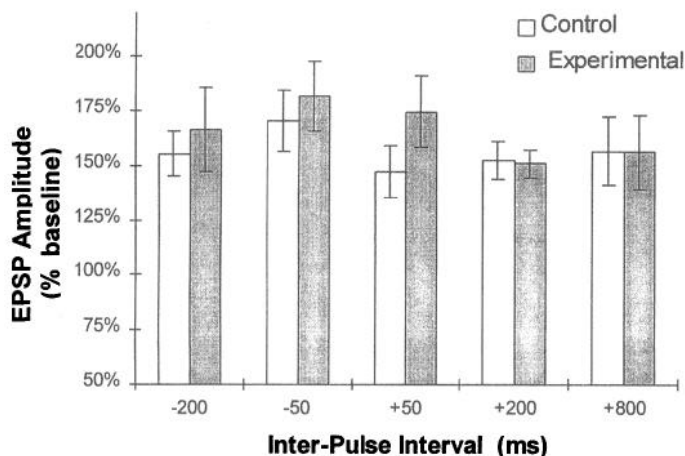
FIG. 3. Average degree of facilitation 30 min after training, from all 5 different interpulse intervals: −200 ($n = 5$), −50 ($n = 6$), +50 ($n = 10$), +200 ($n = 9$), and +800 ($n = 8$). There was no significant difference between the control and experimental group at any of the interpulse intervals examined. Error bars represent means ± SE

Given the time-varying nature and the complex temporal structure of our sensory environment, at least two temporal aspects of Hebbian plasticity are of interest: *1*) The importance of the sequential relationship between pre- and postsynaptic activity and *2*) whether or not associative synaptic plasticity is primarily conjunctive or correlative (Brown et al. 1990).

It has previously been shown that associative LTP in CA1 neurons does exhibit order sensitivity (Gustafsson et al. 1987). Presynaptic activity can precede the postsynaptic depolarizing pulse by 100 ms and still result in the induction of LTP; if however, the presynaptic pulse follows the offset of the depolarizing pulse by 100 ms, LTP is not induced. This temporal asymmetry is a result of the long binding time of glutamate on the *N*-methyl-D-aspartate (NMDA) receptor (Clements et al. 1992). The fact that associative LTP does exhibit order sensitivity has been used to suggest that LTP may provide a neural mechanism for classical conditioning. Presynaptic activity represents the conditioned stimulus (CS) and postsynaptic activity represents the unconditioned stimulus (US). The order sensitivity of LTP would account for the need of the CS to precede the US, and the fact that backward conditioning is generally ineffective.

One of the goals in the current paper was to examine whether or not associative synaptic plasticity in CA1 neurons is conjunctive or correlative (Brown et al. 1990). If synaptic plasticity in dependent solely on the co-occurrence of pre- and postsynaptic activity, plasticity can be considered conjunctive. If however, synaptic plasticity requires a positive correlation between pre- and postsynaptic activity, plasticity is considered correlative. The issue of conjunctive versus correlational plasticity is analogous to the issue of contingency in classical conditioning. Contingency refers to how good of a predictor the CS is of the US. If most of the CSs and USs co-occur, then contingency is high. If in addition to paired CSs and USs, either the CSs and USs also occur independently (i.e., unpaired) contingency is low, resulting in less effective conditioning. For example, if one group of animals receives 10 CS-US pairings, and a second group receives the same number of pairings plus 10 additional

unpaired CS presentations, the second group will exhibit less conditioning. This occurs because for the second group the CS is not as good of a predictor of the US, even though the CS was still paired 10 times with the US (e.g., Mackintosh 1983; Rescorla 1968).

To our knowledge, the issue of how unpaired activity (''contingency'') effects the induction of associative LTP has not been previously examined. However various studies have examined a related issue: whether or not unpaired or anticorrelated activity induces Long-term disability (LTD). Unpaired postsynaptic activity has been shown to produce LTD (Christofi et al. 1993; Kerr and Abraham 1993; Pockett et al. 1990). Stanton and Sejnowski (1989) have reported that anticorrelated activity can produce LTD. However, three labs (Kerr and Abraham 1993; Paulsen et al. 1993) have shown that LTD is not induced by anticorrelated activity. Experiments by Debanne et al. (1994) suggest that synaptic plasticity is sensitive to temporal structure. By using hippocampal slice cultures, they showed that either LTP or LTD could be induced, depending on the interval between postsynaptic and presynaptic activity. If presynaptic activity followed the offset of postsynaptic depolarization by a few hundred milliseconds, LTD was induced. These results suggest that at least under some conditions, synaptic mechanisms that are sensitive to unpaired activity are in place.

In contrast to previous studies, here we have examined the effects of *both* paired and unpaired activity on the induction of associative synaptic plasticity. One might expect from the results of Debanne et al. (1994) that because unpaired activity produced LTD, unpaired presynaptic pulses presented in addition to paired activity might attenuate the degree of LTP. However, our results clearly show that the presence of unpaired presynaptic activity does not decrease the magnitude of associative plasticity induced. One could argue that a decrease was not observed because the degree of facilitation was saturated, and the effects of unpaired activity were masked by the saturated LTP. This is unlikely,
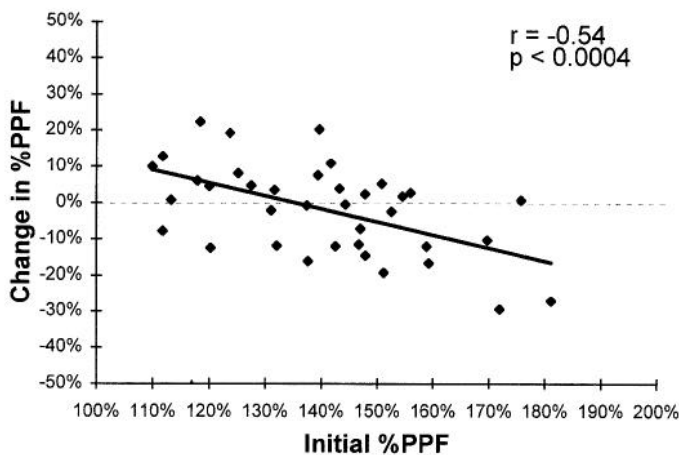

FIG. 4. Inverse correlation between paired-pulse facilitation (PPF) and long-term potentiation (LTP). A plot of the initial degree of PPF vs. PPF 30-min after the induction of LTP shows that the changes in PPF are inversely correlated to initial PPF. Initial %PPF is defined as the ratio of the 2nd and 1st excitatory postsynaptic potential (EPSP) during baseline, multiplied by 100. Change in %PPF was defined as %PPF 30-min LTP minus the initial %PPF. Points represent cells from all intervals except the +800-ms group.

because our protocol did not produce maximal LTP. In 4/4 cases tested, the control group could be further potentiated by additional pairings. Furthermore, inducing less LTP could also mask an effect by not permitting resolution of a slight decrease in LTP in the experimental path.

These results suggest that associative plasticity is primarily conjunctive rather than correlative, and thus insensitive to contingency. Indeed, previous work in the *Aplysia* sensory-to-motor neuron synapse has shown that associative plasticity in that synapse is also insensitive to contingency (Buonomano and Byrne 1990). However, it still remains to be determined whether or not unpaired postsynaptic activity presented in addition to paired activity has any effect on the induction of associative LTP.

Changes in PPF

Average PPF has been reported not to change with LTP in CA1 neurons (Kauer et al. 1988; Manabe et al. 1993; Muller and Lynch 1988; Zalutzky and Nicoll 1990), with one exception (Kuhnt and Voronin 1994). Results from Schulz et al. (1994), analyzing field EPSPs, also indicate that on average PPF does not change, but that there is an inverse correlation between the initial degree of PPF and the degree of PPF after the induction LTP. In other words, LTP tends to decrease PPF if it was initially high, and increase PPF if it was initially low. In the present study, we were able to *1*) examine changes in PPF at intervals of 50 and 200 ms, after pairing-induced LTP; and *2*) examine the possibility that changes in PPF may be dependent on a Hebb-like mechanism; i.e., PPF may increase if the second pulse was paired with depolarization, and decrease if the first pulse was paired.

In agreement with previous studies (Kauer et al. 1988; Manabe et al. 1993; Muller and Lynch 1988; Zalutzky and Nicoll 1990) we observed no average change in the degree of PPF. However, in agreement with the study of Schulz et al. (1994), there was an inverse correlation between the initial and final degree of PPF. The observed changes in PPF were independent of whether or not it was the first or second pulse that was paired with postsynaptic activity, indicating that it is unlikely that changes in PPF are sensitive to whether or not the first or second pulse was paired with depolarization.

Analysis of the interaction between PPF and LTP has been used to argue that the locus of synaptic plasticity is either pre- or postsynaptic. In the present study, it would be difficult to argue for either pre- or postsynaptic mechanisms. First, previous studies implicitly assume that PPF solely results from presynaptic mechanisms, and that the mechanisms underlying PPF and LTP would interact. Furthermore there is evidence that other factors may contribute to PPF such as axonal recruitment (Storm and Lipowsky 1994; D. V. Buonomano, unpublished observations). Second, our experiments were performed with intact inhibition, making it difficult to rule out the possibility of changes in inhibitory components. However, independent of the locus of the changes it is clear that under some conditions, PPF may change as a result of LTP. Thus from a computational perspective, theoretical models that have proposed roles for PPF must take into account the possible changes in PPF as a result of LTP.

Theoretical implications

To date few models have examined the effectiveness of Hebbian plasticity for temporal tasks, i.e., tasks with time-varying stimuli in which critical features are represented in time rather than space, and in which time is not transformed into a spatial code at an earlier processing stage. We have previously described an artificial neural network model in which the elements incorporate paired-pulse facilitation and slow inhibitory postsynaptic potential (IPSPs). This model was able to solve temporal tasks, such as interval discrimination (Buonomano and Merzenich 1995). When Hebbian plasticity was incorporated into the network, there was a generalized decline in performance. One reason for this decline was that Hebbian or associative plasticity reinforced those connections in which the pre- and postsynaptic elements were most often coactive. An interval discrimination task requires determining whether or not two brief pulses are separated by a short or long interval, e.g., 100 or 150 ms. In such a task, the connections most often coactive are those activated by the first pulse, which was common to all possible intervals. Thus, many elements of our network became more responsive to the first pulse, which was devoid of any temporal information. Progressively fewer elements responded preferentially to the second pulse, which contained temporal information, thus impairing temporal processing. These results were obtained by using a conjunctive rule. Specifically coactive neurons underwent an increase in synaptic strength, and total synaptic input onto an element was normalized, providing a competitive mechanism.

Associative synaptic plasticity has proven to be a very powerful learning rule for spatial tasks. However, the current results taken together with previous theoretical results suggest that it is likely that learning rules that are sensitive to temporal structure will be necessary to permit the processing of time-varying stimuli. Future research will have to determine whether there are conditions in which associative synaptic plasticity is sensitive to temporal structure, or whether other forms of plasticity perhaps operating on inhibitory elements are sensitive to temporal features of stimuli.

REFERENCES

BROWN, T. H., KAIRESS, E. W. AND KEENAN, C. L. Hebbian synapses: biophysical mechanisms and algorithms. *Annu. Rev. Neurosci.* 13: 475–511, 1990.
BUONOMANO D. V. AND BYRNE, J. H. Extra Post-training unconditioned stimuli do not decrease associative plasticity in a cellular analogue of contingency in *Aplysia*. *Soc. Neurosci. Abstr.* 16: 596, 1990.
BUONOMANO, D. V. AND MERZENICH, M. M. Temporal information transformed into a spatial code by a neural network with realistic properties. *Science Wash. DC* 267: 1028–1030, 1995.
CLEMENTS, J. D., LESTER, R. A. J., TONG, G., JAHR, C., AND WESTBROOK, G. L. The time course of glutamate in the synaptic cleft. *Science Wash. DC* 258: 1498–1502, 1992.

CHRISTOFI, G., NOVICKY, A. V., BOLSOVER, S. R. AND BINDMAN, L. J. The postsynaptic induction of nonassoociative long-term depression of excitatory synaptic transmission in rat hippocampal slices. *J. Neurophysiol.* 69: 219–29, 1993.

DEBANNE, D., GAHWILER, B. H., AND THOMPSON, S. M. Asynchronous pre- and postsynaptic activity induces associative long-term depression in area CA1 of the rat hippocampus. *Proc. Natl. Acad. Sci. USA* 91: 1148–1152, 1994.

GRATSKI, K. A. AND MERZEVICH, M. M. Hebb-type dynamics is sufficient to account for the inverse magnification rule in cortical somatotopy. *Neural Comput.* 2: 71–84, 1990.

GUSTAFSSON, B., WIGSTRÖM, H., ABRAHAM, W. C., AND HUANG, Y. Y. Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. *J. Neurosci.* 7: 774–780, 1987.

KAUER, J. A., MALENKA, R. C., AND NICOLL, R. A. A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. *Neuron* 1: 911–917, 1988.

KELSO, S. R., GANONG, A. H. AND BROWN, T. Hebbian synapses in the hippocampus. *Proc. Natl. Acad. Sci. USA* 83: 5326–5330, 1986.

KERR, D. S. AND ABRAHAM, W. C. Comparison of associative and non-associative conditioning procedures in the induction of LTD in CA1 of the hippocampus. *Synapse* 14: 305–313, 1993.

KIRKWOOD, A. AND BEAR, M. F. Hebbian synapses in visual cortex. *J. Neurosci.* 14: 1634–1645, 1994.

KIRKWOOD, A., DUDEK, S. M., GOLD, J. T., AIZEMAN, C. D. AND BEAR, M. F. Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. *Science Wash. DC* 260: 1518–1521, 1993.

KUHNT, U. AND VORONIN, L. L. Interaction between paired-pulse facilitation and long-term potentiation in area CA1 of guinea-pig hippocampal slices: application of quantal analysis. *Neuroscience* 62: 391–397, 1988.

MANABE, T., WYLLIE, D. J. A., PERKEL, D. J., AND NICOLL, R. A. Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. *J. Neurophysiol.* 70: 1451–1459, 1993.

MACKINTOSH, N. J. *Conditioning and Associative Learning.* New York: Oxford University Press, 1983.

MULLER, D. AND LYNCH, G. Long-term potentiation differentially affects two components of synaptic responses in hippocampus. *Proc. Natl. Acad. Sci. USA.* 85: 9346–9350, 1988.

PAULSEN, O., LI, Y-G., HVABLY, O., ANDERSEN, P. AND BLISS, T. V. P. Failure to induce long-term depression by an anti-correlation procedure in area CA1 of the rat hippocampal slice. *Eur. J. Neurosci.* 5: 1241–1246, 1993.

POCKETT, S., BROOKES, N. H., AND BINDMAN, L. J. Long-term depression at synapses in slices of rat hippocampus can be induced by bursts of postsynaptic activity. *Exp. Brain Res.* 80: 196–200, 1990.

RESCORLA, R. A. Probability of shock in the presence and absence of a conditioned stimulus in fear conditioning. *J. Comp. Physiol. Psychol.* 66: 1–5, 1968.

SASTRY, B. R., GOH, J. W., AND AUEUNG, A. Associative induction of post-tetanic potentiation in CA1 neurons of rat hippocampus. *Science Wash. DC* 232: 988–990, 1986.

SCHULZ, P. E., COOK, E. P., AND JOHNSTON, D. Changes in paired-pulse facilitation suggest presynaptic involvement in long-term potentiation. *J Neurosci.* 14: 5325–5337, 1994.

STANTON, P. K. AND SEJNOWSKI, T. J. Associative long-term depression in the hippocampus induced by Hebbian covariance. *Nature Lond.* 339: 215–218, 1989.

STORM, J. F. AND LIPOWSKY, R. Evidence that excitability changes in pre-synaptic fibers may affect paired-pulse facilitation in hippocampal slices. *Soc. Neurosci. Abstr.* 20: 1339, 1994.

WIGSTRÖM, H., GUSTAFSON, B., HUANG, Y-Y., AND ABRAHAM, W. C. Hippocampal long-term potentiation is induced by pairing single afferent volleys with intracellularly injected depolarizing pulses. *Acta. Physiol. Scand.* 126: 317–319,.1986.

ZALUTSKY, R. A. AND NICOLL, R. A. Comparison of two forms of long-term potentiation in single hippocampal neurons. *Science Wash. DC* 248: 1619–1624, 1990.