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Hebbian synapses in hippocampus

(Hebb's postulate/long-term potentiation/synaptic enhancement/brain slices)

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ABSTRACT **A combination of current- and voltage-clamp techniques applied to hippocampal brain slices was used to evaluate the role of postsynaptic electrogenesis in the induction of associative synaptic enhancement. In accordance with Hebb's postulate for learning, repetitive postsynaptic spiking enabled enhancement in just those synapses that were eligible to change by virtue of concurrent presynaptic activity. However, the essential postsynaptic electrogenic event that controlled the enhancement was shown to involve biophysical processes that were unknown when Hebb formulated his neurophysiological postulate. The demonstrated spatiotemporal specificity of this pseudo-Hebbian conjunctive mechanism can account qualitatively for the known neurophysiological properties of associative long-term potentiation in these synapses, which in turn can explain the "cooperativity" requirement for long-term potentiation.**

Hebb's (1) neurophysiological postulate for learning proposes that the strength of plastic synapses can be enhanced if the use of those synapses is associated with the nearly simultaneous occurrence of postsynaptic spiking (see ref. 2 for review). Variations of this simple conjunctive mechanism have been invoked to explain or simulate aspects of perceptual (3, 4) and motor learning (5), Pavlovian conditioning (6, 7), cortical associative memory (3, 8, 9), and experiential influences on visual system development (2, 3, 10–12). In spite of the considerable historical and contemporary interest in this hypothesized form of use-dependent synaptic modification, there has been no direct experimental demonstration that Hebbian synapses exist (2, 13).

In the present study we examined the possibility that a Hebbian conjunctive mechanism might underlie associative long-term potentiation (LTP) in regio superior of the hippocampus (ref. 14; see also refs. 15–17). Brief, high-frequency stimulation of a weak synaptic (W) input to this region induces a persistent synaptic enhancement in that pathway only if another, sufficiently strong synaptic (S) input to the same region is activated at about the same time (refs. 14, 18–20; see also refs. 15–17). In a manner reminiscent of Pavlovian conditioning, associative LTP can be selectively induced in either of two separate W inputs by varying the temporal relationship between their activity relative to activity in the S input (20). The mechanism underlying associative LTP has been proposed to mediate certain of the suspected mnemonic functions of the hippocampus (20).

These features of associative LTP can easily be explained by a Hebbian mechanism. According to this interpretation, the postsynaptic currents produced by stimulating the S input allow the required coincidence between activity in the W input and the postsynaptic cell. An alternative possibility is that the essential contribution of activity in the S input is unrelated to consequences of postsynaptic depolarization but instead involves the concomitant release of a critical amount of a necessary "LTP factor" (ref. 21, cf. ref. 22). To evaluate these possibilities, in the present experiments we substituted for the usual S input a combination of current- and voltage-clamp procedures that either *forced* or *prevented* simultaneous pre- and postsynaptic activity.

MATERIALS AND METHODS

Preparation and Maintenance of Slices. Hippocampal slices were prepared from male Sprague–Dawley rats in the usual manner (14, 20, 23) and maintained at 30–32°C in a perfusion chamber. The bathing medium contained (in mM) NaCl, 125; KCl, 2; NaH_2PO_4, 1.25; $MgSO_4$, 4; $CaCl_2$, 3; $NaHCO_3$, 126; and D-glucose, 10. Picrotoxin (10 μM) was added to the bathing medium to block inhibitory synaptic transmission (14, 23–26).

Stimulation Procedures. Either one or two bipolar nichrome stimulating electrodes were placed in the stratum radiatum to stimulate Schaffer collateral/commissural fibers projecting to area CA1 (14, 18–20). Current intensities delivered to the stimulating electrodes were adjusted to evoke subthreshold excitatory postsynaptic potentials (EPSPs) that were 3–6 mV in amplitude at a membrane potential of −80 mV. When two of these W inputs were used, the amplitudes were adjusted to be approximately equal at the start of the experiment. Each was tested every 12 sec with one input following the other by 6 sec. The synaptic stimulation pattern used to induce LTP consisted of five trains each at 100 Hz for 200 msec. For a given synaptic input, each 200-msec train was presented at 12-sec intervals. Unless otherwise indicated, stimulation trains presented to the two synaptic inputs were always separated by 6 sec.

Recording Procedures. Intracellular electrodes, which had resistances of 40–70 MΩ, were filled with 3 M KCl and sometimes also contained 50 mM QX-222 (Astra Pharmaceutical, Worcester, MA), a positively charged lidocaine derivative that blocks sodium but not calcium spikes when injected intracellularly (27–29). QX-222 was iontophoretically injected by passing outward current steps. Intracellular current- and voltage-clamp recordings were obtained from the stratum pyramidale of region CA1 using a single-electrode clamp device operating on a 30% duty cycle and a 2–4 kHz switching rate (see refs. 23–26 for procedural details). The sampled current and voltage were digitized (10 kHz) for on-line and off-line computer (IBM XT) analysis. Cell penetrations were considered acceptable if the resting potential was −60 mV or more negative, the input resistance was 30 MΩ or greater, and there were overshooting action potentials (except when blocked by QX-222 injection). Thirty-seven cells met these criteria throughout the entire experimental protocol.

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Abbreviations: EPSP, excitatory postsynaptic potential; LTP, long-term potentiation; S, strong synaptic; W, weak synaptic.

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RESULTS

Direct Demonstration of the Conjunctive Mechanism. The first set of experiments showed that the presence or absence of coincident postsynaptic activity can control the induction of LTP. A W input was repetitively stimulated (100 Hz for 200 msec) under either of two extreme conditions—while applying a voltage clamp (−80 mV) to the soma of the postsynaptic neuron to prevent postsynaptic spiking and somatic depolarization (Fig. 1*A*, left traces) or while applying simultaneous depolarizing current steps (1.5 nA) to force spiking in the postsynaptic neuron (Fig. 1*A*, right traces). The synaptic response amplitudes to single-shock stimulations were continuously tested under current-clamp conditions (Fig. 1*B*, top traces) and sometimes under voltage-clamp conditions (Fig. 1*B*, lower traces).

The EPSP amplitudes throughout all stages of this experiment are plotted in Fig. 1*C*. Neither postsynaptic activity alone (Depol. Alone) nor synaptic stimulation conducted while applying a voltage clamp to the postsynaptic cell soma (100 Hz + Voltage-Clamp) produced LTP. A second synaptic stimulation conducted while applying a voltage clamp again failed to induce LTP. However, when presynaptic stimulation was paired with simultaneous postsynaptic spiking (100 Hz + Depol.) LTP *was* induced, and it lasted until the end of the experiment (Fig. 1 *B* and *C*). Similar results were obtained in 11 other cells, 10 of which were studied using the differential conditioning paradigm to be described.

Spatial Specificity of the Conjunctive Mechanism. The second set of experiments further demonstrated that the synaptic enhancement was specific, or limited, to just those synapses that were stimulated during the depolarization-induced spiking. Using a differential conditioning paradigm (18–20), the spatial specificity of the conjunctive mechanism was demonstrated by showing selective enhancement in only one of two separate sets of synaptic inputs (W1 and W2) to a neuron. Both W1 and W2 inputs were first alternately stimulated (100 Hz for 200 msec) while applying a voltage clamp (−80 mV) to the postsynaptic neuron. The results from 10 neurons (Fig. 1*D*, *Left*) showed that there was little change in either input. Both inputs were then restimulated in the same fashion, but this time stimulation of W1 input was paired with a simultaneous depolarizing current step whereas W2 input was stimulated while applying a voltage clamp as before. The results from these same 10 neurons illustrate (Fig. 1*D*, *Right*) that LTP was induced in W1 but not the W2 pathway. Fifteen minutes after the repetitive stimulation, the mean increase in EPSP from W1 inputs (87%) was significantly greater than the mean increase from W2 inputs (4%) ($t = 3.8$, df = 9, $P < 0.05$).

Because of the experimental design, we could not be certain whether voltage clamping selectively *blocked* LTP in one input or passing outward current selectively *enabled* LTP in the other input. To distinguish between these two possibilities, we examined five additional neurons using the same

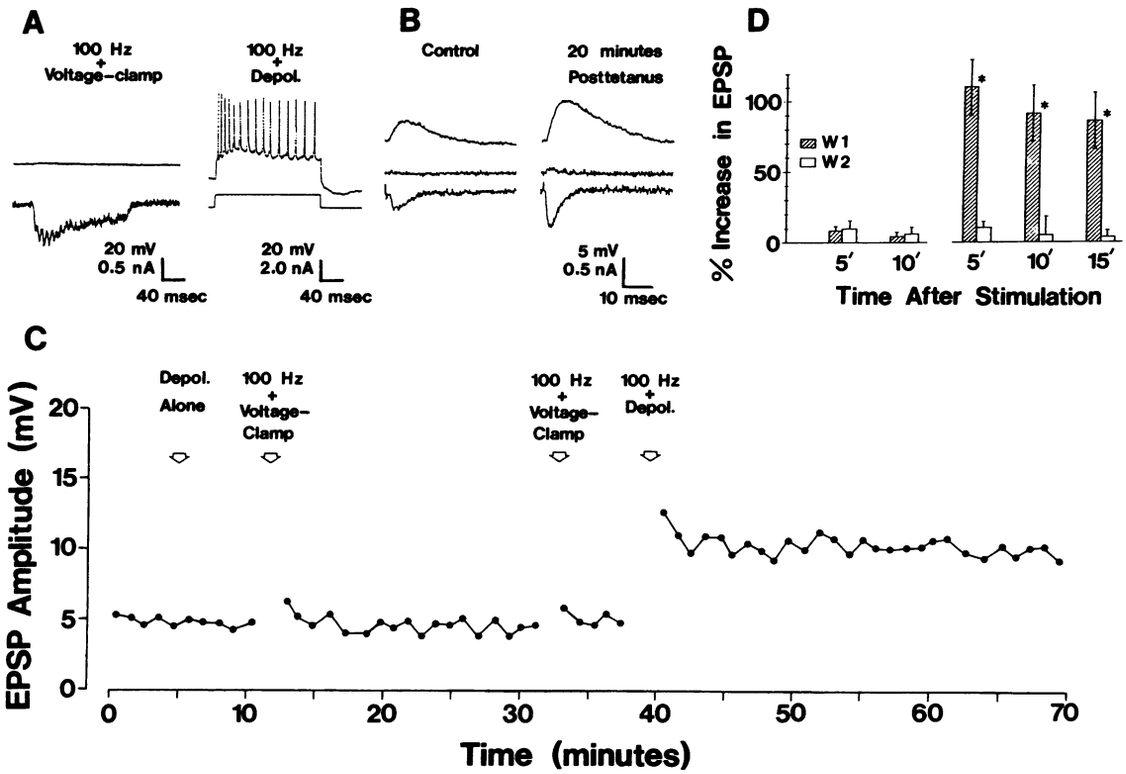

FIG. 1. Direct demonstration of the conjunctive mechanism. (*A*) (*Left*) Voltage-clamp record of inward synaptic currents (lower trace) and membrane potential control (upper trace) during the synaptic stimulation train. (*Right*) Current-clamp recording of postsynaptic spiking (upper trace) produced by an outward current step (lower trace) which is paired with the synaptic stimulation train. (*B*) Computer average of five single synaptic responses recorded under current-clamp (upper traces) or voltage-clamp (middle traces show potential control and lower traces show synaptic currents) conditions. (*Left*) Responses during the initial control period. (*Right*) Responses 20 min after pairing synaptic stimulation with the outward current step. (*C*) EPSP amplitudes as a function of the time of occurrence (arrows) of three manipulations—an outward current step alone (Depol. Alone) or synaptic stimulation trains delivered while applying either a voltage clamp (100 Hz + Voltage-Clamp) or while applying an outward current step (100 Hz + Depol.). Each point is the average of five consecutive EPSP amplitudes. (*D*) Mean increases in the EPSPs produced by two synaptic inputs (W1 and W2) at the indicated times after stimulation. (*Left*) W1 and W2 were alternately presented stimulation trains while applying a voltage clamp to the postsynaptic cell. (*Right*) W1 pathway was stimulated during application of an outward current step and W2 pathway was stimulated during application of a voltage clamp to the postsynaptic cell. Asterisks denote significant differences ($P < 0.05$) between the changes induced in the W1 and W2 responses (paired *t* test for dependent means).

paradigm except that a voltage clamp was *not* applied during stimulation trains. We found that stimulation of W1 or W2 inputs alone was not sufficient to induce LTP in either pathway, in accordance with previous studies of W inputs to these neurons (refs. 14, 18–20; see also refs. 15–17). As in the preceding experiments, LTP was selectively induced only in the synaptic input (W1) that was stimulated during depolarization-induced postsynaptic spiking. The differences in the experimentally produced changes in the two synaptic inputs, measured 15 min after tetanic stimulation (50% mean increase for W1 versus 1% increase for W2), were statistically significant ($t = 3.8$, df = 4, $P < 0.05$). Based on these results, in the following experiments a voltage clamp was not applied during synaptic stimulation.

Temporal Specificity of the Conjunctive Mechanism. In the third set of experiments, the temporal specificity of the conjunctive mechanism was examined by varying the intervals between postsynaptic depolarization and presynaptic stimulation of either of two synaptic inputs. High-frequency stimulation (100 Hz for 200 msec) of W1 and W2 inputs (separated by 220 msec) followed 6 sec later by postsynaptic depolarization-induced spiking (Fig. 2*A1*) did not result in LTP in either synaptic input (Fig. 2*B*, part *A1*). Postsynaptic activity following W1 by 10 msec and preceding W2 by 10 msec (Fig. 2*A2*) also failed to result in LTP in either synaptic input (Fig. 2*B*, part *A2*). However, when postsynaptic depolarization was paired simultaneously with either W1 stimulation (Fig. 2*A3*) or with W2 stimulation (Fig. 2*A4*), LTP was selectively induced in the paired synaptic input (Fig. 2*B*, parts *A3* and *A4*).

The results from 15 neurons demonstrated that there is a narrow temporal window within which postsynaptic depolarization can enable the induction of LTP. This is evident from the relationship between the interstimulus interval (ISI) and the amount of synaptic enhancement, where the ISI is defined as the time from the onset of presynaptic stimulation

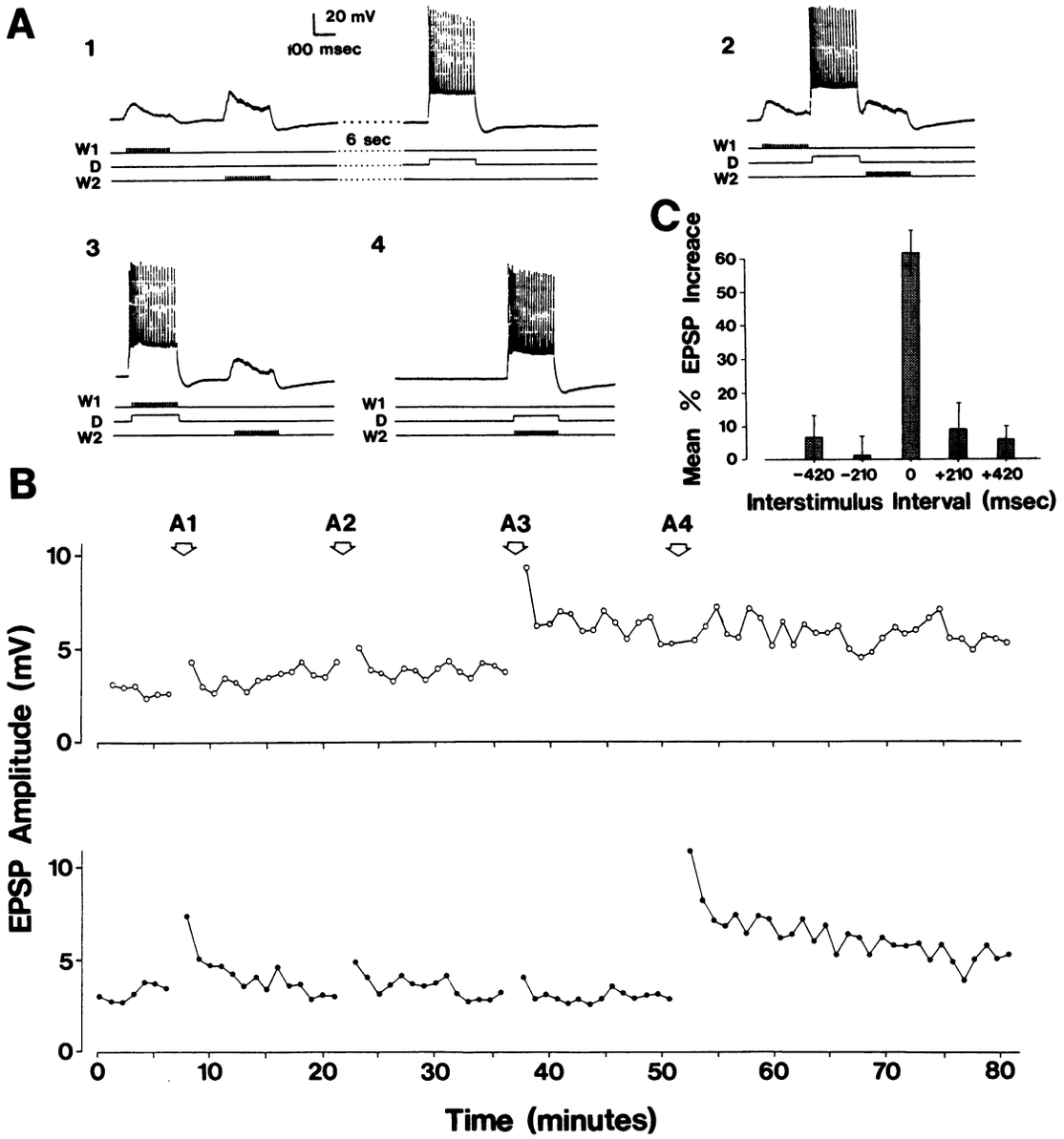

FIG. 2. Temporal constraints on the conjunctive mechanism. (*A*) Four different paradigms (*A1–A4*) that vary the interval between stimulation of either of two weak synaptic (W1 and W2) inputs and the presentation of an outward current step. Periods of synaptic stimulation (lines labeled W1 and W2) and the depolarizing current step (line labeled D) are indicated below each postsynaptic voltage trace. (*B*) EPSP amplitudes produced by W1 (○) and W2 (●) inputs. The four experimental treatments (parts *A1–A4*) are indicated by arrows. Each point is the average of five responses. (*C*) Temporal specificity of the conjunctive mechanism. Results are from 25 pathways in 15 neurons.

to the onset of postsynaptic depolarization. Of the five ISIs that were tested in these experiments (Fig. 2*C*), only an ISI of 0 msec was effective in producing LTP (62% mean increase).

Role of Sodium Spikes in the Conjunctive Mechanism. The fourth set of experiments demonstrated directly that the conjunctive mechanism does not require postsynaptic sodium spikes. Results from five cells that were injected with QX-222 indicated that postsynaptic depolarization can enable LTP in the absence of high-frequency sodium spiking that normally accompanies a large depolarization. In these experiments, the EPSP amplitudes produced by two synaptic inputs (W1 and W2) were continuously monitored by alternately testing each input every 6 sec. Two seconds after each single test shock to W1 input and 4 sec before each test of W2 input a depolarizing current step was administered. This pattern of testing was repeated throughout the experiment except when repetitive synaptic stimulation of W1 and W2 pathways was substituted for the single test shocks (Fig. 3*A*). When W1 and W2 inputs were repetitively activated, the depolarizing current step was delivered at one of three times—2 sec after stimulating W1 and 4 sec before stimulating the W2 input (Fig. 3*A1*), during W1 stimulation (Fig. 3*A2*), or during W2 stimulation (Fig. 3*A3*; waveforms shown expanded).

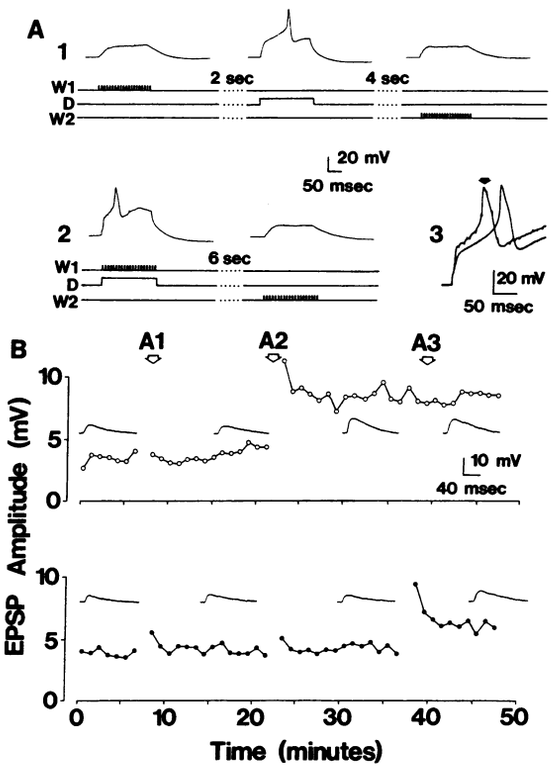

FIG. 3. Demonstration that the conjunctive mechanism does not require the elicitation of sodium spikes (in a neuron injected with QX-222). (*A*) Three different paradigms (*A1–A3*) that varied the timing of the depolarizing current step (indicated on line D) in relationship to the stimulation of either of two weak synaptic inputs (indicated on lines W1 and W2). (*A1*) There was no temporal overlap between synaptic stimulation and the current step. (*A2*) Stimulation of W1 pathway was simultaneously paired with the current step. (*A3*) Stimulation of W2 pathway was simultaneously paired. The expanded and superimposed waveforms compare the postsynaptic response that occurred when synaptic stimulation was simultaneously paired with the current step (arrow) with the waveform produced by the current step alone (no arrow). (*B*) EPSP amplitudes produced by W1 (○) or W2 (●) as a function of the three experimental manipulations (parts *A1–A3*), which occurred at the indicated times (arrows). Each point is the average amplitude of five EPSPs.

Following the injection of QX-222, the depolarizing current step failed to elicit the usual train of brief sodium spikes, but instead it elicited a waveform that may result in part from a voltage-dependent calcium current (cf. refs. 27–29). In comparison with the usual sodium spikes (Figs. 1*A* and 2*A*), the onset latency of this QX-222-resistant waveform was much greater and its duration was considerably longer (Fig. 3*A1*). When the outward current step was paired with synaptic stimulation, the onset of this QX-222-resistant response was briefer (Fig. 3*A3*), but the amplitude and waveform were similar with (Fig. 3*A3*, arrow) or without (Fig. 3*A3*, no arrow) concomitant synaptic stimulation.

The results of this complete experiment are plotted in Fig. 3*B*, where the upper graph (open symbols) shows the EPSP amplitudes and selected waveforms produced by the W1 input and the lower graph (solid symbols) gives the same information for the W2 input. When the depolarizing outward current step was presented during the interval between synaptic stimulation of W1 and W2 pathways (Fig. 3*A1*), LTP was not induced in either synaptic input (Fig. 3*B*, part *A1*). However, when the depolarizing current step was paired with synaptic stimulation of W1 input (Fig. 3*A2*), LTP was selectively induced in the W1 response (Fig. 3*B*, part *A2*). When postsynaptic depolarization was subsequently paired with synaptic stimulation of W2 input (Fig. 3*A3*), the amplitude of the EPSP produced by the W2 input was enhanced (Fig. 3*B*, part *A3*). The magnitude of the enhancement was similar to that observed when sodium spikes were not blocked. In the five cells studied, paired stimulation of the W1 input produced a 72% mean increase in the EPSP response to W1 input, whereas unpaired stimulation of W2 resulted in a 6% mean increase of EPSP in the W2 pathway (measured during part *A2* of each experiment).

DISCUSSION

These experiments demonstrate that synaptic enhancement can be rapidly and selectively induced in either of two synaptic inputs to hippocampal neurons depending on the temporal relationship between presynaptic activity and postsynaptic depolarization (Figs. 1 and 2). The results reveal directly that the elicitation of postsynaptic sodium spikes is not necessary for the conjunctive mechanism to operate (Fig. 3). The essential postsynaptic electrogenic event must therefore involve some other consequence of depolarization, such as calcium influx (30). These findings confirm and explain previous inferences that postsynaptic depolarization somehow contributes to LTP induction (31) but that the elicitation of postsynaptic (sodium) spikes may not be necessary (32). The results are neutral in regard to which side of the synaptic cleft undergoes those modifications that ultimately cause the expressed enhancement (cf. refs. 33–35).

The results support the proposal that the essential contribution of the S input in enabling the occurrence of LTP in a simultaneously active W input is simply to supply a critical amount of postsynaptic depolarization. The spatiotemporal specificity of the conjunctive mechanism revealed here appears sufficient to account for the demonstrated specificity of associative LTP in this region of the hippocampus (refs. 14, 18–20; cf. refs. 15–17). The properties of associative LTP (refs. 14, 18–20; see also refs. 15–17) in turn can explain the "cooperativity" requirement (36, 37) for LTP in this region. Cooperativity refers to the fact that, in some synaptic systems, the probability or magnitude of LTP is an increasing function of the number of simultaneously stimulated afferent inputs to a neuron. Independent results leading to similar conclusions were recently published by Wigström and coworkers (38), who further showed that high-frequency stim-

ulation of the presynaptic elements is unnecessary for the conjunctive mechanism to operate.

Are these Hebbian synapses? The results are possibly compatible with the spirit of certain modern formulations of Hebb's postulate. Levy and Desmond (7) use the term "Hebbian" in reference to conjunctive mechanisms in which synaptic enhancement is some (yet undefined) quantitative function of the relationship between presynaptic activity and concurrent postsynaptic depolarization. Contemporary usage varies (cf. refs. 2–13, 21, 37) and bears a tenuous relationship to what Hebb (1) actually stated (p. 62): "When an axon of cell A is near enough to excite cell B or repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." Our results demonstrate directly that the underlying biophysical mechanism does not require "firing" the postsynaptic cell—if this is taken to mean the elicitation of the usual sodium spike. One might therefore prefer to regard these hippocampal synapses as being pseudo-Hebbian—recognizing that under some circumstances (Figs. 1 and 2) they will behave in a manner consistent with several modern formulations of Hebb's postulate (2, 3, 7, 9–13) but that the essential postsynaptic electrogenic event involves some consequence of dendritic depolarization other than the elicitation of a sodium spike in the soma (Fig. 3). The latter distinction may prove to be important. As more is learned about the underlying molecular mechanisms, a better terminology and classification scheme will emerge.

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