Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 1148–1152, February 1994
Neurobiology

Asynchronous pre- and postsynaptic activity induces associative long-term depression in area CA1 of the rat hippocampus *in vitro*

(calcium/*N*-methyl-D-aspartate/long-term potentiation/synaptic plasticity/learning)

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Communicated by Leon N Cooper, September 23, 1993 (received for review August 11, 1993).

ABSTRACT **Associative long-term depression (LTD) was induced in hippocampal slice cultures with repeated low-frequency (0.3 Hz) stimulation of the Schaffer collateral pathway, only when such stimuli were preceded by intracellular injection of brief depolarizing current pulses in the postsynaptic CA1 pyramidal cell. The decrease in excitatory postsynaptic potential amplitude lasted >30 min, could be reversed by induction of potentiation, could be induced at previously potentiated inputs, was input-specific, and did not require activation or potentiation of other inputs. The magnitude of the depression depended upon the time interval between depolarization and stimulation and upon the duration of the depolarizing pulse. LTD was not observed in neurons impaled with electrodes containing a Ca^{2+} chelator. LTD could not be induced in the presence of an *N*-methyl-D-aspartate receptor antagonist, suggesting that voltage-dependent Ca^{2+} influx is necessary but not sufficient for LTD induction. We conclude that associative LTD results when synaptic activity follows postsynaptic depolarization within a circumscribed time window.**

Long-term potentiation (LTP) of excitatory synaptic transmission can be induced homosynaptically with a high-frequency tetanus of afferent fibers (1) or associatively when the activation of one set of synapses is synchronous with the activity of a second set of synapses that are capable of producing a postsynaptic depolarization sufficient to allow Ca^{2+} influx via *N*-methyl-D-aspartate (NMDA)-receptor-gated ion channels (2, 3). The complementary phenomenon of long-term depression (LTD) has also been reported at Schaffer collateral-CA1 pyramidal cell synapses under several different conditions. Homosynaptic nonassociative LTD can be induced with prolonged (3–15 min) stimulation of a single set of synapses at moderate frequencies (1–5 Hz) and requires NMDA-receptor-mediated Ca^{2+} influx (4–6). The requirements for induction of heterosynaptic associative LTD, in which activation of the postsynaptic cell by one set of synapses can cause a decrease in the efficacy of another set of synapses, are less well established. The critical step for the induction of associative LTD may be postsynaptic hyperpolarization (3, 7), postsynaptic depolarization (8, 9), metabotropic glutamate receptor activation (10), moderate postsynaptic Ca^{2+} influx (11, 12), or the induction of LTP in the conditioning pathway (13). Part of the difficulty in defining the cellular basis of associative LTD in the hippocampus and, therefore, elucidating its role in learning and memory stems from the lack of a suitable reproducible protocol for its induction *in vitro* (14, 15). In this paper we characterize the mechanisms that trigger associative LTD by using a convenient stimulation protocol.

MATERIALS AND METHODS

Hippocampal slice cultures were prepared as described (16). After 2–4 weeks *in vitro*, cultures were transferred to a recording chamber on an inverted microscope. Cultures were perfused with warmed (35°C) saline containing 149 mM Na^+, 149 mM Cl^-, 2.7 mM K^+, 2.8 mM Ca^{2+}, 2.0 mM Mg^{2+}, 11.6 mM HCO_3^-, 0.4 mM $H_2PO_4^-$, 5.6 mM glucose, and phenol red (10 mg/liter). Intracellular recordings were obtained from CA1 pyramidal cells using sharp microelectrodes filled with 1 M potassium methyl sulfate. Excitatory postsynaptic potentials (EPSPs) were elicited with stimulation of two distinct inputs using two microelectrodes filled with 155 mM NaCl placed in stratum radiatum, one at the border between areas CA1 and CA3 and another at the subicular end of area CA1 (Fig. 1*A*). Stimuli (0.1 ms, −5 to −15 μA) were always delivered at 0.3 Hz by using intensities that elicited EPSPs of 5–10 mV in amplitude, with no apparent inhibitory synaptic component at membrane potentials of −65 to −75 mV. Prolonged stimulation at this frequency was found to have no effect of its own on EPSP amplitude ($n = 4$ cells; data not shown). EPSP amplitudes were measured from traces averaged each minute. The potentiation and depression of the EPSPs (as percentage control) were identical if the initial slope of the EPSP, rather than its amplitude, was measured. Values of potentiation or depression reported in this study are based on averages of EPSPs over 2–3 min taken 10 min after the end of the pairing procedure. Numerical values in text and graphs are given as the mean ± SEM. The Student *t* test was used for statistics. Because LTP could not be induced in 14 of 48 cultures, only data from cultures in which LTP was observed were considered. All data from these cultures were included in the analysis, however, regardless of the magnitude of LTD.

RESULTS

As previously established for acutely prepared hippocampal slices (17), repeated (50–100 times) pairing of synaptic stimulation of one pathway with simultaneous depolarization of the postsynaptic neuron, elicited with the intracellular injection of depolarizing current pulses (0.5–2.0 nA for 240 ms), resulted in a long-lasting potentiation of that EPSP (Fig. 1*B*, protocol P1). The average increase in EPSP amplitude, 10 min after cessation of the pairing procedure, was 73 ± 20% (Fig. 2*A*) ($P < 0.0001$, paired *t* test; $n = 36$) and was observed to last for >20 min.

If the second pathway was stimulated with some delay after each of the depolarizing pulses used to potentiate the first (paired) pathway, then a long-lasting decrease in the amplitude of the EPSP elicited with stimulation of the second (unpaired) pathway was observed (Fig. 1*B*, protocol P1). Maximal depression occurred with an interval of 800 ms

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Abbreviations: LTP, long-term potentiation; LTD, long-term depression; NMDA, *N*-methyl-D-aspartate; AP5, D-2-amino-5-phosphovalerate; EPSP, excitatory postsynaptic potential; AHP, after hyperpolarization; BAPTA, tetrapotassium bis(*O*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid.

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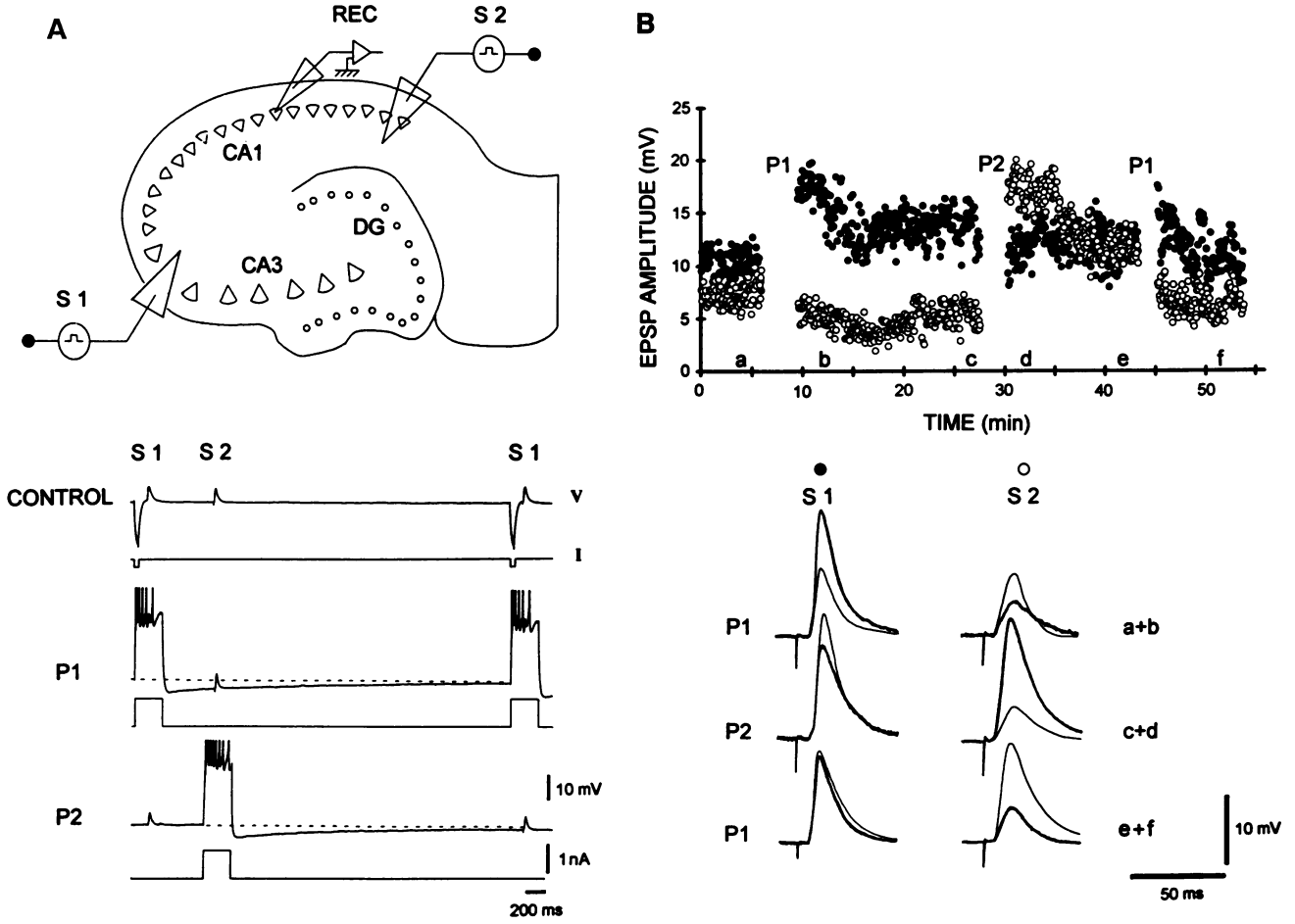

FIG. 1. Induction of LTP and LTD. (*A*) Experimental protocol. Two distinct components of the Schaffer collateral pathway were stimulated alternatively (S1 and S2) to evoke EPSPs of 5–10 mV in CA1 pyramidal cells, with no apparent inhibitory component. The two pathways were stimulated with an interstimulus interval of 800 ms, repeated every 3.3 s. In the first protocol (P1), brief depolarizing current pulses (0.5–1.5 nA, 240 ms) and simultaneous stimulation of the paired input (S1) were followed by stimulation of the unpaired input (S2) 800 ms after the depolarizing pulse. In the second protocol (P2), the depolarizing pulse was paired with stimulation of the previously unpaired input (S2), while the previously paired input (S1) was activated 2400 ms after the depolarizing pulse. In both cases, the pairing procedure was repeated 50–100 times. In some experiments, the P1 protocol was used without stimulation of an input during the depolarization, and we refer to this procedure as post-pulse pairing (see Fig. 2*B*). (*B*) Reversible induction of LTP and LTD. Plot of EPSP amplitude elicited with each input (●, S1; ○, S2) as a function of time. The P1 stimulation protocol produced a potentiation of the paired input (S1) and a depression of the unpaired input (S2). The P2 protocol then induced a potentiation of the previously depressed input (S2) while the previously potentiated input (S1) was slightly depressed. Repetition of the P1 protocol caused a depression in the previously potentiated input (S2) but had no effect on the input already potentiated during the first pairing (S1). EPSPs for each input (taken at the indicated times) before and after each stimulation protocol are shown below (the thicker trace is the response after the pairing protocol).

between the 240-ms depolarizing pulse and synaptic activation, amounted to a 31 ± 4% decrease in amplitude (significantly different from control, unpaired *t* test, $P < 0.0001$, $n = 20$), and lasted for >20 min (Fig. 2*B*). If the unpaired pathway was stimulated >2 s after the 240-ms depolarizing pulse, there was no significant change in EPSP amplitude (−11 ± 6%; $P > 0.01$, unpaired *t* test, $n = 16$ for a 2400-ms delay). There thus appeared to be a strict time window for the association of pre- and postsynaptic activity to induce LTD (see Fig. 4*B*). It was therefore predicted that inactive synapses would not undergo a change in their efficacy. Indeed, if the unpaired pathway was not stimulated during the injection of 240-ms depolarizing pulses, no significant change in EPSP amplitude was observed 10 min later (−1 ± 7%; $P > 0.5$, unpaired *t* test, $n = 7$).

The decrease in EPSP amplitude could be reversed by inducing LTP at previously depressed synapses (Fig. 1*B*, protocol P2) ($n = 6$). Likewise, LTD could be readily induced at synapses that had previously been potentiated (Fig. 1*B*). The amount of depression was not different when induced at naive or potentiated synapses ($P > 0.5$, unpaired *t* test; 36 ± 5% vs. 41 ± 6%; $n = 9$ and 7, respectively). The amount of potentiation, however, was found to be significantly greater at previously depressed synapses than at naive synapses ($P < 0.01$, unpaired *t* test). On average, the potentiation induced at naive synapses was 52 ± 12% ($n = 15$), whereas the potentiation at previously depressed synapses was 170 ± 49% ($n = 6$). This finding suggests that there may be an interaction at the cellular level between the mechanisms responsible for the expression of LTP and LTD (18).

Heterosynaptic nonassociative depression has been described in unstimulated pathways as a result of induction of strong potentiation in other pathways (13). The associative induction of LTD reported here does not depend on the induction of LTP in another pathway, however. (*i*) In experiments in which both paired and unpaired pathways were stimulated (using the P1 protocol of Fig. 1*A*), there was no significant correlation between the magnitude of the potentiation of the input paired with the depolarization and the depression of the unpaired input ($P > 0.5$, *F* test, $n = 20$). (*ii*) Stimulation protocols in which only one input was stimulated 800 ms after each 240-ms depolarizing current pulse (post-

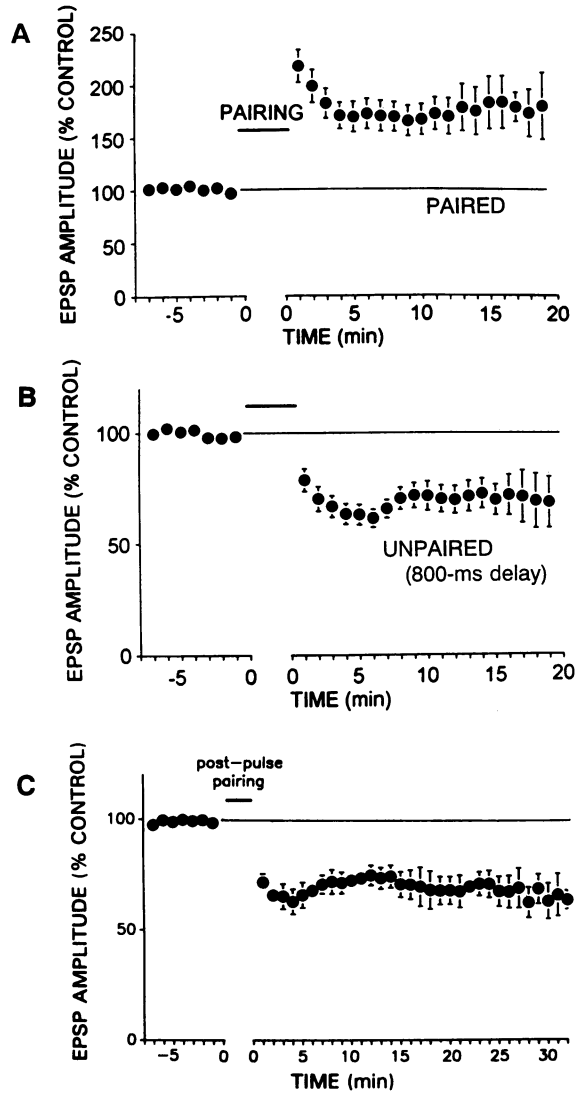

FIG. 2. Characteristics of LTP and LTD evoked with 240-ms pulses. (*A*) Stable LTP of EPSPs evoked with the paired input averaged 73% of the control amplitude in 36 experiments, including both naive and previously depressed inputs. (*B*) Stable LTD of the unpaired input averaged −31% of the control amplitude in 20 experiments when LTP was induced in the other pathway (see *A*). (*C*) Pooled data from 11 experiments showing LTD elicited with the post-pulse pairing protocol (repeated stimulation of only one input 800 ms after each pulse). LTD elicited with this protocol is not different from that elicited with the protocol in which LTP is simultaneously induced at another input (see *B*).

pulse pairing) also induced a depression of EPSP amplitude (32 ± 3%; n = 11; Fig. 2*C*), which was not significantly different ($P > 0.5$, unpaired t test) from that observed when stimulation of a second input was paired with postsynaptic depolarization (see Fig. 2*B*). It is thus postsynaptic depolarization itself that is necessary for induction of associative LTD and not potentiation of an independent input, as suggested (8, 9).

Depolarizing current pulses cause a pronounced after hyperpolarization (AHP) in hippocampal pyramidal cells. The possibility that synaptic activation coupled with postsynaptic hyperpolarization is the trigger for the induction of LTD in our experiments was tested by repeatedly (100 times) pairing stimulation of one input with injection of hyperpolarizing current pulses (−0.5 to −2.0 nA, 240 ms) via the recording electrode. After such stimulation protocols, however, the EPSP amplitude was observed to be not significantly different than control (89 ± 5%; $P > 0.01$, paired t test, n = 7) (see ref. 7). Furthermore, activation of the unpaired input 50 ms after the depolarizing pulse, a time when the AHP reaches its maximal amplitude, produced weak LTP, not LTD (see Fig. 4*B*).

Induction of homosynaptic LTD is blocked by either NMDA receptor antagonists or strong chelators of intracellular Ca^{2+} (4, 5). To establish the trigger for the induction of associative LTD, we first reduced the increase in the postsynaptic free Ca^{2+} concentration during the induction protocol by injecting the Ca^{2+} chelator tetrapotassium bis-(*O*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′,-tetraacetic acid (BAPTA, 25 mM) from the recording electrode. At this concentration, the Ca^{2+}-activated K^+ conductance underlying the AHP was blocked within 5 min, and it was not possible to induce either LTP or LTD (EPSP amplitude = 94 ± 4% and 102 ± 3% of control; unpaired t test, $P > 0.1$ and $P > 0.5$, n = 4 and 7, respectively). To ensure that the effects of BAPTA were examined in truly "plastic" cultures, recordings were made from the same cultures without BAPTA in the intracellular electrode. In these experiments, pairing of depolarization and synaptic activation produced a 65 ± 25% potentiation of EPSP amplitude (n = 3). Elevation of the intracellular Ca^{2+} concentration is, therefore, required for the induction of associative LTD.

The role of NMDA receptors in the induction of LTD was tested with bath application of the selective antagonist D-2-amino-5-phosphovalerate (AP5, 40 μM). Consistent with previous observations in acutely prepared hippocampal slices using weak stimuli (19, 20), AP5 produced a 40 ± 12% (n = 6) decrease in EPSP amplitude at resting membrane potential under control conditions (Fig. 3*A*). Nonetheless, pairing postsynaptic depolarization with stimulation of one pathway in the presence of 40 μM AP5, while simultaneously stimulating a second pathway 800 ms after each depolarizing pulse, did not result in either potentiation of the paired input or depression of the unpaired input. When the same cells and inputs were assessed after washout of AP5, however, a significant depression of the unpaired EPSP amplitude (38 ± 9%; $P < 0.01$, paired t test, n = 6) was observed (Fig. 3 *B* and *C*). NMDA receptor activation is, therefore, required for the induction of associative LTD.

There are two sources of Ca^{2+} influx with this stimulation protocol: voltage-dependent and NMDA-receptor-gated. If the amount of voltage-dependent Ca^{2+} influx during the depolarizing pulses is important for triggering LTD, then decreasing the duration of the depolarizing pulse should influence the induction of LTD by decreasing the size and duration of the intracellular Ca^{2+} transient produced by each pulse. When pulses of 240-ms duration were used, no change in EPSP amplitude was observed with an interval of 400 ms, whereas maximal LTD was obtained with an 800-ms interval (Fig. 4*B*). In contrast, there was a 25 ± 4% decrease in amplitude for EPSPs stimulated 400 ms after a 50-ms depolarizing pulse but only a 12 ± 3% decrease for EPSPs stimulated 800 ms after the pulses (Fig. 4*A*) ($P < 0.0001$ and $P < 0.05$, unpaired t test, n = 5 and 5, respectively). The amount of Ca^{2+} influx elicited with the 50-ms pulses was significantly less, as shown by the failure of simultaneous synaptic activation to result in LTP (Fig. 4*B*) (mean change in amplitude = −8 ± 3%; n = 3 cells). Increasing the duration of the depolarizing pulse to 240 ms led, however, to significant ($P < 0.005$, paired t test, n = 3) potentiation of the synchronously active EPSP in these same cells by 52 ± 16%.

DISCUSSION

These experiments demonstrate the importance of voltage-dependent Ca^{2+} influx for the initiation of associative LTD and support earlier suggestions (11, 12, 21) that the sign of the

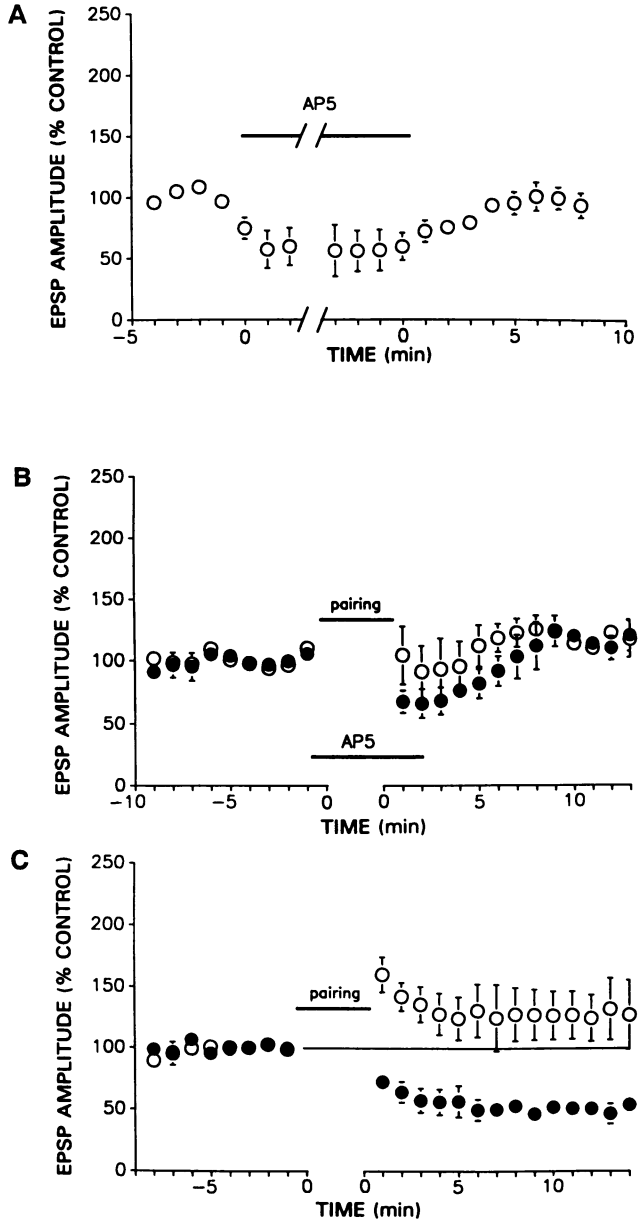

FIG. 3. NMDA receptors and LTD induction. (*A*) Bath application of the NMDA receptor antagonist AP5 (40 μM) caused a 40% depression of EPSP amplitude ($n = 6$). The amplitude recovered to the initial level 5 min after washout. (*B* and *C*) AP5 prevents LTP and LTD. (*B*) Pooled data showing failure to induce either LTP, at inputs that were paired with depolarizing current pulses (○), or LTD, at inputs stimulated 800 ms after the depolarization (●) (117 ± 8% and 107 ± 9% of the control amplitude 10 min after pairing, respectively) in the presence of AP5 ($n = 6$). Note that the transient decrease of EPSP amplitude is due to the depressant action of AP5 (see *A*). (*C*) Fifteen minutes after washout of AP5, LTP (35 ± 15%) and LTD (38 ± 9%; $P < 0.01$, unpaired t test) were induced in the same neurons as in *B* with the identical stimulation protocol.

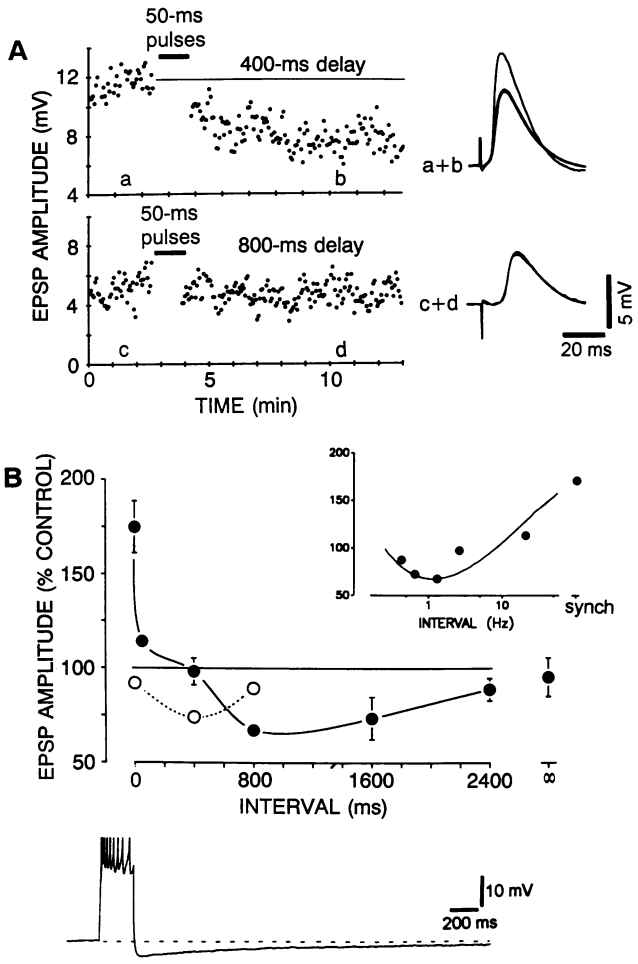

FIG. 4. Induction of LTD is dependent on pulse duration. (*A*) Post-pulse pairing (repeated 100 times) of 50-ms depolarizing pulses with stimulation of two distinct inputs after each pulse induced LTD only with the shorter of the two intervals (400 ms) and not with the longer interval (800 ms). EPSPs taken at the indicated times are shown superimposed at right. (*B*) Summary of change in EPSP amplitude as a function of the time interval between synaptic activation and the depolarizing pulses, either 50 ms (○) or 240 ms (●) in duration. For the 240-ms pulses, LTP was obtained with simultaneous synaptic activation and postsynaptic depolarization, whereas a delay of 800 or 1600 ms resulted in LTD ($n = 20$ and 6). The changes in EPSP observed when an input was stimulated ≥2400 ms after depolarization or not stimulated during the pairing procedure (infinite interval) were not significantly different from control. Synaptic activation shortly (50 ms) after the 240-ms depolarization elicited weak potentiation. A typical AHP after a 240-ms depolarizing pulse is illustrated below the graph. Note that neither the size nor the sign of the change in EPSP amplitude correlates with the amplitude of the AHP. After 50-ms depolarizing pulses, in contrast, no significant LTP was obtained with simultaneous pairing ($n = 3$) and a weak LTD was obtained with an 800-ms interval ($n = 5$). Strong LTD could only be elicited with a 400-ms interval ($n = 5$). The data for the EPSP amplitude (as percentage control) after asynchronous pairing with 240-ms pulses have been replotted (*Inset*) as a function of the instantaneous frequency to facilitate comparison with homosynaptic LTD (4). Low frequencies led to LTD, whereas higher frequencies or synchronous activity (synch) resulted in LTP.

change in synaptic strength is determined by the size of the increase in the intracellular Ca^{2+} concentration. When combined with stimulation of afferent inputs, small or moderate increases result in long-lasting depression, whereas larger increases produce potentiation, in agreement with previous studies in neocortical neurons (21–23). Moderate activation of NMDA receptors by the test input, which was observed with low-frequency stimulation during the control period (Fig. 3*A*), did not result in depression of the EPSP, unless such stimuli were preceded by depolarizing pulses. Presumably, the increase in intracellular Ca^{2+} mediated by NMDA receptors alone at this frequency was insufficient to trigger the biochemical events responsible for LTD. When preceded by depolarizing pulses, however, the NMDA-receptor-mediated Ca^{2+} influx and the voltage-dependent Ca^{2+} influx could be summated to induce LTD. Furthermore, depolarization-induced Ca^{2+} influx, while necessary, must not be sufficient by itself to induce LTD because no depression in

EPSP amplitude was produced by asynchronous pairing in the presence of AP5, and LTD was not obtained when the synapses were inactive. The association between NMDA-receptor-dependent and voltage-dependent Ca^{2+} influx confers an important property on associative LTD: neither the magnitude of LTD nor the intervals at which it can be obtained are fixed, but rather they both vary as a function of the total amount of voltage-dependent and NMDA-receptor-mediated Ca^{2+} influx (Fig. 4*B*).

We conclude that associative LTD will be triggered *in situ* when a conditioning input repeatedly produces an increase in intracellular Ca^{2+} that is less than that required to initiate LTP. Evidence for such processes has previously been presented. In the heterosynaptic "out-of-phase" stimulation protocol (3, 8), long-lasting depression of a test input can be induced when stimulation of the test pathway is repeatedly (50 times) alternated with a short tetanus (100 Hz for 50 ms) to a separate pathway. Like the depolarizing pulses used in our experiments, it is likely that the brief tetanus produces an elevation of intracellular Ca^{2+} that does not fully decay to the resting level when the test pathway is activated (24–26). Previous difficulties in eliciting LTD with this protocol may tentatively be attributed to an incorrect temporal (Fig. 4*B*) or spatial (27) relationship between the test and conditioning inputs. LTD induction has also been reported when postsynaptic hyperpolarization is used during a weak tetanus (5–10 Hz), keeping the size of the postsynaptic calcium influx in a range favoring induction of LTD and not LTP (3, 6).

In the homosynaptic LTD protocol, a low-frequency tetanus (1–3 Hz) is applied to the test pathway, probably eliciting an increase in intracellular Ca^{2+} that is subthreshold for the induction of LTP but sufficient to induce LTD of the test input. It is thus probable that homosynaptic LTD represents an "autoassociative" variant of the same phenomenon. Indeed, when the change in EPSP amplitude in the present experiments is plotted as a function of the interval between pre- and postsynaptic activity, measured as instantaneous frequency (Fig. 4*B Inset*), there is a remarkable correlation between the frequencies of stimulation that are effective in inducing LTD in the homosynaptic protocol (4) and the effective intervals in our experiments. Moreover, the relationship between pre- and postsynaptic activity is comparable to the theoretical predictions of Bienenstock *et al.* (28).

The conditions necessary for the induction of LTP, synchronous synaptic activity, and postsynaptic depolarization can be said to confirm Hebb's rule, which states that simultaneous pre- and postsynaptic activity leads to an increase in synaptic strength. Stent (29) postulated a correlate to Hebb's rule: "When the presynaptic axon of cell A repeatedly and persistently fails to excite cell B while cell B is firing . . . , changes take place . . . such that A's efficiency, as one of the cells firing B, is decreased." The form of LTD we describe here demonstrates that presynaptic activity is necessary for the associative induction of long-lasting decreases in the efficacy of synaptic transmission at those synapses, provided such activity is not synchronous with postsynaptic depolarization. Furthermore, our results add an element of specificity to LTD by placing a tight temporal limit on the delay between firing in cell B and presynaptic activity in the axon of cell A that will permit LTD to develop, indicating that not all asynchronously active or inactive synapses will become depressed. Moreover, this interval is not fixed but is rather a function of the amount of cell B's activity.

We thank F. Grogg, L. Rietschin, and R. Schöb for their assistance; Dr. Y. Frégnac for sharing his unpublished results; and Drs. U. Gerber, M. Scanziani, M. Capogna, and R. D. Traub for helpful comments on the manuscript. This work was supported by the Sassella Foundation, the Dr. Eric Slack-Gyr Foundation, and the Swiss National Science Foundation (Grant 31-27641.89).

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