R. Ransom, *Glia* **1**, 64 (1988)]. Whole-cell currents were recorded with standard patch-clamp techniques with recording pipettes of 1-megohm resistance (dc) and were low pass–filtered at 2 kHz. Fast application of different agonists in high Na^+ or high Ca^{2+} extracellular solutions with a double-barreled application pipette was as described (*5*). Most of the experiments were performed on fusiform cells attached to the bottom of the culture dish and oriented parallel to the solution stream. In a few experiments, the cells were lifted from the bottom of the dish. The *I-V* relations of agonist-induced currents were obtained with voltage ramps 2 s in duration. Normal rat Ringer solution consisted of 135 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, and 5 mM Hepes at pH 7.2 (with NaOH). High Na^+ extracellular solution was 140 mM NaCl, 1 mM $MgCl_2$, and 5 mM Hepes at pH 7.2 (with NaOH). High Ca^{2+} extracellular solution was 110 mM $CaCl_2$ and 5 mM Hepes at pH 7.2 [with $Ca(OH)_2$]. Pipette solution was 140 mM CsCl, 10 mM EGTA, and 10 mM Hepes at pH 7.2 (with CsOH).

Apparent permeability ratios P_{Ca}/P_{Cs} were calculated as described (*15*) from average values of reversal potentials; we assumed biionic conditions and used the following ion concentrations: 140 mM Cs^+ and 110 mM Ca^{2+}.

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Hebbian Depression of Isolated Neuromuscular Synapses in Vitro

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Modulation of synaptic efficacy may depend on the temporal correlation between pre- and postsynaptic activities. At isolated neuromuscular synapses in culture, repetitive postsynaptic application of acetylcholine pulses alone or in the presence of asynchronous presynaptic activity resulted in immediate and persistent synaptic depression, whereas synchronous pre- and postsynaptic coactivation had no effect. This synaptic depression was a result of a reduction of evoked transmitter release, but induction of the depression requires a rise in postsynaptic cytosolic calcium concentration. Thus, Hebbian modulation operates at isolated peripheral synapses in vitro, and transsynaptic retrograde interaction appears to be an underlying mechanism.

In formulating a cellular mechanism underlying the temporal specificity in associative learning, D. O. Hebb (*1*) postulated that the coincidence of electrical activities in the pre- and postsynaptic cells helps modulate the strength of the synaptic connection. Extensions (*2*) of Hebb's postulate suggest that synaptic efficacy may be potentiated or stabilized by synchronous pre- and postsynaptic activities but weakened by asynchronous activities. This Hebbian mechanism has been used to account for several forms of synaptic plasticity in mature and developing central nervous systems (*3*), but whether it operates at peripheral synapses is unknown. We investigated whether Hebbian modulation occurs at isolated neuromuscular synapses in culture, where the simplicity of the cellular environment facilitates the study of its mechanisms.

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Isolated myocytes innervated by single cocultured spinal neurons in 1-day-old *Xenopus laevis* nerve-muscle cultures (*4*) were used (Fig. 1A). In the first set of experiments, the postsynaptic myocyte was repetitively activated by iontophoretic application of acetylcholine (ACh) pulses to the myocyte surface near the synapse either synchronously or asynchronously with suprathreshold stimulation of the presynaptic neuron. The membrane current of the myocyte was monitored by whole-cell voltage-clamp recording (*5*). The amplitude and duration of the ACh pulses were adjusted to produce a membrane current equal to that of a usual impulse-evoked postsynaptic current (EPC). We assayed the synaptic efficacy by measuring the EPC amplitude before and after repetitive coactivation (Fig. 1, B and C). During the first 10-min control period, the mean amplitude of EPCs elicited by low-frequency test stimuli remained relatively constant. The mean EPC amplitude was unaffected by synchronous coactivation (100 stimuli at 2 Hz). In contrast, coactivation with the same number of stimuli but applied asynchronously to the same synapse with a delay of 100 ms between the post- and presynaptic activation, reduced the EPC amplitude. The result was the same regardless of whether the synchronous coactivation was applied before or after the asynchronous one.

The temporal specificity of coactivation in producing synaptic depression was revealed by a series of experiments in which the presynaptic stimulation was applied either at or ± 10, ± 63, ± 125, and ± 250 ms after the onset of each ACh pulse applied to the myocyte (Fig. 1D). With no delay (synchronous coactivation), depression was not observed. Small but significant depression was found when a ± 10-ms interval was imposed between the pre- and postsynaptic stimuli. The effect increased to a maximum of about 50% at intervals above 63 ms. This critical dependence of synaptic depression on the asynchrony between pre- and postsynaptic activation agrees with the expected temporal specificity in Hebbian modulation. In these experiments, the myocyte was voltage-clamped at the resting potential during repetitive coactivation to allow assessment of the induced membrane current at the myocyte. Similar results were obtained when the myocyte was held in current-clamp condition, allowing depolarization of the myocyte membrane potential (*6*).

We next tested whether synaptic depression required postsynaptic ACh receptor activation, presynaptic stimulation, or both. Repetitive postsynaptic iontophoresis of ACh in the absence of presynaptic stimuli induced synaptic depression similar to that induced by the asynchronous coactivation. Significant depression was observed when the myocyte was held in either voltage-clamp or current-clamp condition during ACh application, which suggests that postsynaptic receptor activation in the absence of synchronous presynaptic activity was sufficient to induce synaptic depression (Fig. 2A). Thus, presynaptic activation is not required. Furthermore, presynaptic suprathreshold stimulation (100 pulses at 2 Hz) alone did not result in significant depression ($n = 4$), which indicates that asynchronous postsynaptic activation is not only sufficient but also necessary for the induction of depression.

The depression induced by asynchronous postsynaptic activation was long lasting (Fig. 2B). Pulses of ACh were applied in current-clamp condition, and synaptic responses were monitored for 20 min after ACh application. No significant recovery of synaptic responses was observed. Persistent depression was observed in all four cases for which synaptic responses were monitored for 1 hour after ACh applica-

tion. In comparison, we observed no significant change in synaptic efficacy when ACh pulses were not applied. The extent of synaptic depression induced by repetitive postsynaptic activation depended at least in part on the number of ACh pulses applied (Fig. 2C). Up to 60% of depression was observed after a single episode of 100 ACh pulses. When more episodes of ACh pulses were applied to the same myocyte, we observed further depression of the synaptic response (n = 5).

The synaptic depression could be a result of a reduction in the evoked ACh release or in the postsynaptic ACh sensitivity or both. Application of 100 pulses of ACh at the myocyte surface did not change the muscle ACh sensitivity at either the stimulated site or an adjacent site (n = 4) (Fig. 3A), as assayed by two ACh iontophoretic pipettes separated by 5 to 10 μm (7). The possibility that ACh sensitivity at the subsynaptic sites was selectively reduced was also excluded, as the amplitude distribution of miniature excitatory postsynaptic currents (MEPCs) was unaffected by the repetitive ACh application that induced significant depression of the EPCs (Fig. 3B). The mean amplitude of MEPCs after ACh application was 101 ± 5% (± SEM; n = 5) of the control values. Statistical analysis of the distribution of MEPC amplitudes confirmed that the spontaneous events remained unaffected by the postsynaptic activation (Fig. 3B). The MEPC frequency also showed no significant change (102 ± 8% of control values ± SEM; n = 5) after application of ACh pulses under voltage-clamp conditions.

The constancy of the mean amplitude of spontaneous events suggests that the reduction of evoked synaptic responses is likely to result from a reduced quantal content of ACh secretion. We tested this idea by analyzing the fluctuation of evoked responses (8). We assumed that evoked synaptic transmission is quantal in nature and that the variation of EPC amplitudes can be described by binomial distribution modified to account for the variability of the quantal size. Given this assumption, the ratio v/m^2, where m and v are the mean EPC amplitude and its variance, respectively, is a quantity independent of the quantal size and remains constant if the change in EPC is a result solely of the postsynaptic change in ACh sensitivity. On the other hand, if synaptic depression results from some presynaptic mechanisms, the v/m^2 value will increase after depression. We found that v/m^2 values were consistently larger for different degrees of depression (Fig. 3C). Thus, presynaptic reduction of quantal content appears to be the most likely cause of synaptic depression.

Because synaptic depression can be induced by asynchronous ACh application to a myocyte that was voltage-clamped at the resting potential, postsynaptic depolarization is not necessary for the induction of synaptic depression. Repetitive activation of muscle ACh receptors, however, could induce substantial elevation of the cytosolic Ca^{2+} concentration, either through Ca^{2+} influx or release from internal stores (9), even in the presence of the voltage clamp. We examined the importance of postsynaptic Ca^{2+} elevation by loading the myocyte with Ca^{2+} buffer 1,2-*bis*(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA; 5 mM) through the whole-cell recording pipette. The BAPTA is a Ca^{2+} buffer with fast binding kinetics that effectively prevents changes in cytosolic Ca^{2+} (10). In all experiments using the BAPTA-containing recording pipette, we failed to observe synaptic depression after repetitive applications of ACh (100 pulses, 2 Hz), either alone or in the presence of asynchronous presynaptic activation (Fig. 4). Thus, a rise in the Ca^{2+} concentration within the myocyte cytoplasm is necessary for the induction of synaptic depression. The importance of Ca^{2+} influx at postsynaptic cells in the induction of

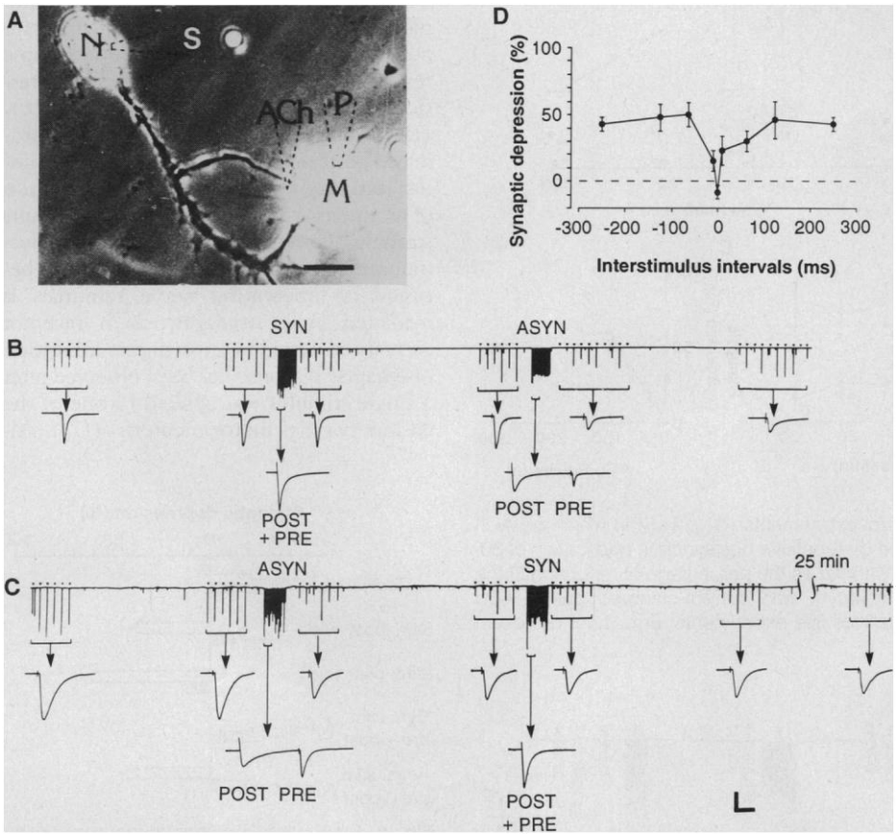

Fig. 1. Effects of synchronous and asynchronous coactivation on synaptic efficacy. (**A**) Phase-contrast micrograph of an isolated neuromuscular synapse in a 1-day-old *Xenopus* culture. A spherical myotomal myocyte (M) was innervated by a cocultured spinal neuron (N). Also marked are positions for the whole-cell patch-recording pipette (P), the extracellular stimulating pipette (S), and the iontophoretic ACh pipette (ACh). Bar = 20 μm. (**B**) Result from a coactivation experiment in which the presynaptic neuron was stimulated at the soma to fire action potentials either synchronously (SYN) or asynchronously (ASYN) at the same frequency (2 Hz, 100 pulses) as the postsynaptic ACh application. In the latter situation, each ACh pulse was applied 100 ms before the presynaptic stimulation. The continuous trace depicts the membrane current recorded from an innervated myocyte under voltage-clamp condition [holding potential (V_h) = −70 mM, filtered at 150 Hz, inward current downward]. The EPCs were elicited at the times marked by the small dots. Insets depict computer-averaged evoked membrane currents at a higher time resolution (filtered at 2.5 kHz) for the recording periods pointed to by the arrows. Scales: slow traces, 2 nA, 50 s; fast traces, 2 nA, 15 ms (test EPCs) and 30 ms (coactivation currents). (**C**) Same as (B), except that the asynchronous coactivation was applied before the synchronous one. (**D**) The dependence of synaptic depression on the time interval between pre- and postsynaptic activation (both for 100 stimuli at 2 Hz). Synaptic depression is defined as the percentage of reduction in the mean EPC amplitude after coactivation as compared to that of the same synapse before coactivation. Each point represents the average value obtained from 5 to 14 synapses. Error bars represent SEM. Asynchronous coactivations at all time intervals are significantly different from synchronous coactivation ($P < 0.05$, Mann-Whitney U test).

long-term potentiation (LTP) in the hippocampus is well established (*11*). Evidence suggests that the maintenance of LTP involves at least in part a potentiation of evoked transmitter release (*8*, *12*), as a result of transsynaptic action of a retrograde factor or factors released by the postsynaptic cell (*13*). The synaptic depression we observed also required postsynaptic Ca^{2+} elevation and involved presynaptic modulation of transmitter release, but the retrograde factor or factors apparently resulted in a persistent negative regulation.

Heterosynaptic depression occurs in the hippocampus for inputs that are inactive or weakly active (*14*). Associative long-term depression can be induced by negatively correlated pre- and postsynaptic activities in a manner that follows the Hebbian rule (*15*). Our finding suggests that Hebbian synaptic depression may be a general property of synapses and can be observed at isolated synapses in culture. In the *Xenopus* cultures used in the present study, synapses made by two co-innervating nerve terminals may undergo activity-dependent competition: tetanic stimulation of one synapse results in immediate and persistent suppression of the unstimulated synapse (*16*). Here, the iontophoretic ACh pulses produced postsynaptic membrane currents similar to those induced by tetanic stimulation of an innervating neuron. Thus, our results strongly support the notion that tetanus-induced heterosynaptic suppression between co-innervating nerve terminals is mediated by postsynaptic ACh receptor activation. Rapid heterosynaptic inhibition of synaptic response has been observed after a single stimulus was applied to one of the co-innervating motor neurons (*17*). Al-

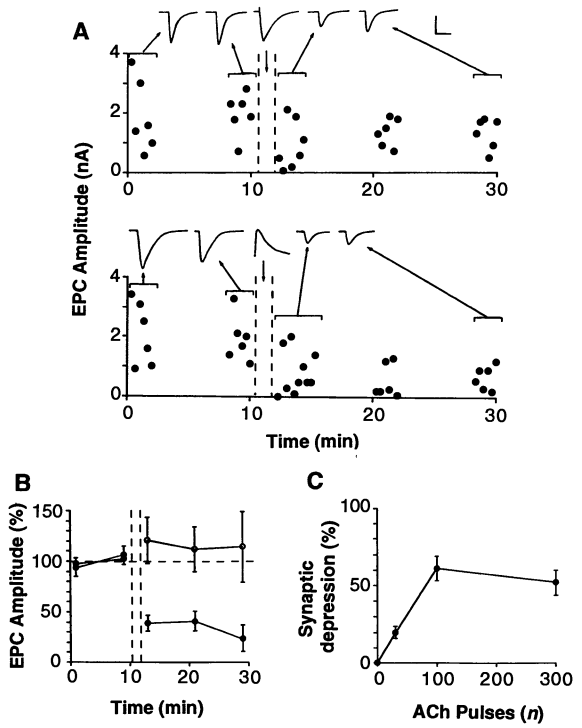

Fig. 2. Synaptic depression induced by postsynaptic ACh receptor activation in the absence of presynaptic stimulation. (**A**) The EPC amplitudes were plotted versus time after the ACh pulses were applied to the myocyte (at 2 Hz for 50 s) during the period between the two dashed lines. During the ACh application, the myocytes were held in either voltage-clamp (V_h = −70 mV; upper graph) or current-clamp (lower graph) condition. Insets above depict computer-averaged EPCs and myocyte membrane currents (upper) or potentials (lower) induced by the ACh pulses. Scales: 1 nA, 20 ms (EPCs and ACh-induced currents); 20 mV, 60 ms (ACh-induced depolarization). (**B**) Time course of synaptic depression. Normalized mean EPC amplitudes were plotted versus time for five experiments after 100 ACh pulses (2 Hz) were applied (●) under current-clamp condition (during the period marked by the two dashed lines). The mean EPC amplitude before application of ACh was set at 100%. Error bars represent SEM. Also shown are data from control experiments (○; n = 5) in which no ACh pulses were applied. (**C**) Synaptic depression induced by repetitive postsynaptic application of 30, 100, and 300 ACh pulses (all at 2 Hz). Depression is defined as the percentage of reduction in the mean EPC amplitude after ACh application. The myocyte was current-clamped during ACh application. Each point represents the average value from five experiments. Error bars represent SEM.

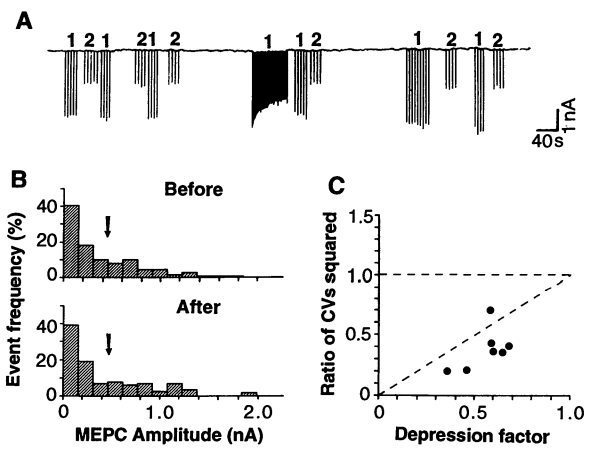

Fig. 3. Tests for pre- versus postsynaptic mechanisms of synaptic depression. (**A**) Repetitive application of ACh pulses by two iontophoresis pipettes (1 and 2) to assay ACh sensitivity at two adjacent sites (5 to 10 μm apart) on the surface of an uninnervated myocyte. Inward membrane currents (downward deflections) induced by ACh pulses at low frequency (0.1 Hz) through pipettes 1 and 2 are marked 1 and 2, respectively. The frequency of iontophoresis through pipette 1 was then elevated to 2 Hz for 50 s. No significant change of ACh responses was observed at either site after the high-frequency ACh application. (**B**) Amplitude histograms of MEPCs recorded in the experiment shown in the upper graph of Fig. 2A, before and after the repetitive ACh application, normalized as a percentage of total events. Arrows mark the mean amplitude. The two distributions are not significantly different (P > 0.20, Mann-Whitney U test). (**C**) Quantal analysis of EPCs. The ratio of coefficients of variation (CVs) squared before and after depression (CV_b^2/CV_a^2) was plotted versus the depression factor. $CV = v^{1/2}/m$; the depression factor is defined as the ratio of mean EPC amplitudes (after ACh application/before ACh application). Results shown are data collected in seven separate experiments in which large enough numbers of EPCs were recorded.

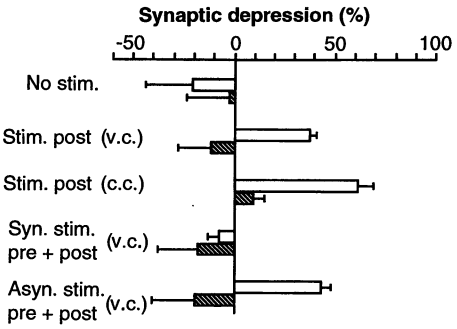

Fig. 4. Prevention of synaptic depression by buffering postsynaptic cytosolic Ca^{2+} with BAPTA. Depression is defined as in Fig. 2C. Each bar represents the average value of the percentage of depression from five synapses. Empty and striped bars represent experiments without and with BAPTA, respectively, in the recording pipette. All stimuli were 100 pulses at 2 Hz. The error bars represent SEM. No stim., controls with no stimulation applied to either the pre- or postsynaptic cell; Stim. post (v.c.), the myocyte stimulated with ACh pulses in voltage-clamp condition (V_h = −70 mV); Stim. post (c.c.), the myocyte stimulated with ACh pulses in current-clamp condition; Syn. stim. pre + post (v.c.), the neuron and the myocyte coactivated synchronously; Asyn. stim. pre + post (v.c.), the neuron and the myocyte coactivated asynchronously, with 250 ms between each presynaptic stimulus and postsynaptic ACh application. The myocyte was voltage-clamped at −70 mV during coactivation.

though more than one mechanism may be involved in the heterosynaptic interaction, postsynaptic ACh receptor activation may be sufficient to mediate the inhibitory action on the unstimulated synapse.

Significant synaptic depression was induced when pre- and postsynaptic stimuli were separated by an interval of only 10 ms. This suggests that the protection rendered by the synchronous synaptic activity against the depression is transient, perhaps lasting only the duration of the synaptic current. The temporal specificity of coactivation in the induction of synaptic depression requires the existence of a sensitive coincidence detection mechanism that controls either the production or the action of the retrograde signal. One possibility is that postsynaptic Ca^{2+} entry results in the release of a transient retrograde factor and that such a factor causes synaptic depression except when presynaptic Ca^{2+} concentration is elevated by synchronous activity. The elucidation of molecular mechanisms underlying the detection of correlated pre- and postsynaptic activities and the retrograde signaling will contribute to the understanding of the nature of synaptic interactions.

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6. Y. Dan and M.-m. Poo, unpublished data.
7. The tips of two pipettes were placed along the perimeter of the spherical myocyte in close contact with the myocyte surface. The diameter of the surface area affected by each of the applied ACh pulses over the duration of ACh-induced current flow (~50 ms) was estimated to be <5 μm. The distance between the pipettes was chosen to be in the range of 5 to 10 μm because this was estimated to be the average distance between the ACh pipette and the synapse in the depression experiments. Greater distance between the pipettes produces less synaptic depression [Y. Dan and M.-m. Poo, *Soc. Neurosci. Abst.* **17**, 1288 (1991)]. The latter result is also consistent with the absence of heterosynaptic suppression induced by repetitive activity if the two synapses are separated by a distance greater than 50 μm (*16*).
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$$m = aNp \text{ and } v = a^2Np(1 - p) + a^2Npc_m^2$$

where a is the average quantal size, N is the total number of available quanta, p is the release probability, and c_m is the coefficient of variation of MEPCs. As a result, $CV^2 = (1 + c_m^2 - p)/(Np)$, where CV is the coefficient of variation defined as $v^{1/2}/m$. If the depression is a result of the reduction of postsynaptic ACh sensitivity, which is expressed as the reduction of a, then CV^2 will not change after depression because it is not a function of a. The ratio CV_b^2/CV_a^2 (where CV_b^2 is the square of the coefficient of variation before depression and CV_a^2 is the square of the coefficient of variation after depression) thus remains the same at all levels of depression, and the points should fall along a horizontal line. However, if the depression results from some presynaptic mechanisms, as indicated by a reduction in N, p, or both, then CV^2 will increase after depression, and the points should fall on or below the diagonal line. This interpretation does not take into consideration more complicated mechanisms; for example, some postsynaptic sites switch from "on" to "off" states after repetitive postsynaptic activation.
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