A TEST OF HEBB'S POSTULATE AT IDENTIFIED SYNAPSES WHICH MEDIATE CLASSICAL CONDITIONING IN *APLYSIA*[1]

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Abstract

In 1949, D. O. Hebb proposed a novel mechanism for producing changes in the strength of synapses that could account for associative learning. According to Hebb, the strength of a synapse might increase when the use of that synapse contributes to the generation of action potentials in a postsynaptic neuron. Thus, an essential feature of this postulate is that action potentials must occur in both a postsynaptic cell and a presynaptic cell for associative synaptic changes to occur. We have directly tested Hebb's postulate in *Aplysia* at identified synapses which are known to exhibit a temporally specific increase in efficacy during a cellular analogue of differential conditioning. We find that the mechanism postulated by Hebb is neither necessary nor sufficient to produce the associative change in synaptic strength that underlies conditioning in *Aplysia*. In contrast, impulse activity in the presynaptic cell must be paired with facilitatory input, supporting the hypothesis that the temporal specificity of classical conditioning in *Aplysia* can be accounted for by activity-dependent amplification of presynaptic facilitation.

In 1949, D. O. Hebb proposed a specific mechanism for producing functional changes at synapses that could contribute to associative learning. Hebb suggested that *alterations in the strength of synapses* might *occur when the use of those synapses* is associated with and *contributes to the generation* of action potentials in the postsynaptic neuron. Specifically, Hebb proposed that: "When an axon of cell A is near enough to excite a cell B and 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."

Although Hebb's original postulate was focused on developmental plasticity such as would occur during the formation of "cell assemblies," it has had a major impact on thinking about the neuronal mechanisms of learning (see for example Marr, 1969; Stent, 1973; Woody et al., 1978; Rauschecker and Singer, 1981; Bienenstock et al.,

1982; Heidmann and Changeaux, 1982). This impact derives from the simple solution Hebb's model offered for two central problems in classical conditioning. First, Hebb's postulate accounts for temporal specificity, the hallmark of associative learning, using plausible physiological mechanisms. Second, it accounts for stimulus and response specificity, which are common features of classical conditioning, without the need of complex neural circuitry.

Hebb envisioned that the most likely physiological mechanism giving rise to the increased synaptic strength was a growth of synaptic "knobs." Thus, although he allowed for other possibilities, Hebb favored the notion that the locus for the plastic changes was presynaptic. In an interesting extension of Hebb's original postulate, Stent (1973) and, more recently, Heidmann and Changeaux (1982) have suggested that the synaptic alteration at a Hebb synapse could involve a change in the sensitivity or the state of activation of the receptors of the postsynaptic cell.

An essential feature of Hebb's original postulate is that, for the associative changes to occur, use of a synapse must contribute to the generation of *action potentials in a postsynaptic neuron*. This aspect of Hebb's postulate has been tested in a variety of neuronal analogues of learning. In some of these studies, postsynaptic activity has been shown to play no role in synaptic plasticity (Kandel and Tauc, 1965; Wurtz et al., 1967). On the other hand, other studies have suggested that postsyn-

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aptic activity may play an important role (O'Brien et al., 1977; Baranyi and Feher, 1981a, b; see also Rauschecker and Singer, 1981). However, in no case has it been possible to relate the change in synaptic efficacy to a specific behavioral instance of associative learning.

Recently, classical conditioning of a simple withdrawal reflex in *Aplysia* has been demonstrated (Carew et al., 1981, 1983), and a specific associative change has been localized to an identified set of synapses between the sensory and motor cells for the reflex (Hawkins et al., 1983a). We have now examined whether the associative change at these synapses depends upon the pairing of presynaptic and postsynaptic activity. We found that the mechanism postulated by Hebb does not contribute to classical conditioning of this withdrawal reflex: impulse activity in the postsynaptic cell is neither necessary nor sufficient to produce the temporally specific change in synaptic efficacy that underlies classical conditioning in *Aplysia*. By contrast, impulse activity in the *presynaptic* cell is critical. These results are consistent with our earlier finding that the temporal specificity of classical conditioning of this reflex may be explained by activity-dependent amplification of presynaptic facilitation (Hawkins et al., 1983a; see also Walters and Byrne, 1983), which is an elaboration of the same mechanism that underlies behavioral sensitization of this reflex (Castellucci and Kandel, 1976; Castellucci et al., 1980; Klein and Kandel, 1978, 1980; Klein et al., 1982).

Materials and Methods

Aplysia californica weighing 100 to 300 gm were obtained from Pacific Biomarine (Venice, CA). Animals were anesthetized with isotonic $MgCl_2$ (50% body weight) prior to surgery. The central nervous system (the pedal, pleural, cerebral, and abdominal ganglia and connectives) was dissected free from the body along with the tail nerves (posterior pedal nerves—P9). The ganglia were then pinned to the Sylgard floor of a Lucite recording chamber, and the nerves from the tail were pinned around Ag-AgCl stimulating electrodes in the chamber. The abdominal ganglion, which contains the siphon sensory and motor neurons, was partially desheathed, and the preparation was washed with normal artificial seawater (Instant Ocean) for approximately 45 min before the experiment. We obtained intracellular recordings using standard techniques (Byrne et al., 1974). A Wheatstone bridge circuit was used for recording and passing current simultaneously. Two siphon sensory neurons in the LE cluster (Byrne et al., 1974) were impaled with glass microelectrodes (5 to 15 megohms, filled with 2.5 M KCl) and caused to fire controlled trains of six action potentials by injecting individual 60-msec depolarizing current pulses at a rate of 12/sec for 0.5 sec. In addition, a siphon motor neuron which received monosynaptic excitatory connections from both of the sensory neurons was impaled (see Fig. 1). In a cellular analogue of the differential conditioning procedure (Carew et al., 1983; Hawkins et al., 1983a), action potentials in one sensory neuron were temporally paired with tail nerve stimulation, while action potentials in the other sensory neuron were specifically unpaired. Thus, the action potentials in

the two sensory neurons served as the paired and unpaired conditioned stimuli (CS^+ and CS^-, respectively), and stimulation of the tail nerve (5-msec biphasic current pulses at 10 Hz for 1.5 sec) served as the unconditioned stimulus (US). Current intensity for the tail shock was set to be just supra-threshold for the production of EPSPs in the motor neuron in response to a single (5-msec) pulse. In some experiments, action potentials produced directly in the postsynaptic motor neuron by injecting a prolonged (1.0 sec) intracellular depolarizing paired and unpaired sensory neurons were counterbalanced across experiments. The EPSPs from both sensory neurons were measured 15 min after training and compared to their respective pretraining amplitudes (for details see Hawkins et al., 1983a).

Statistical analyses were carried out by means of a t test for either correlated means (within-group comparison) or independent means (between-group comparison). All comparisons were two-tailed. All data are reported as means ± SEM.

Results

To explore the role of postsynaptic activity in producing temporally specific changes in synaptic efficacy, we applied to individual nerve cells a differential training procedure based upon the behavioral training procedure that produces differential classical conditioning in *Aplysia* (see "Materials and Methods"). In previous experiments (Hawkins et al., 1983a) this training procedure produced greater facilitation of the EPSP from the paired sensory neuron than from the unpaired neuron. This effect was attributed to differential amplification of presynaptic facilitation of the paired sensory neuron. However, differential facilitation might also have been due to Hebb-type synaptic plasticity since the unconditioned stimulus (shock to the tail or tail nerve), in addition to causing presynaptic facilitation, also produced excitatory synaptic input in the postsynaptic siphon motor neuron (via a polysynaptic pathway; see Walters et al., 1983), causing it to fire action potentials.

To determine the role of postsynaptic activity in conditioning, we explored whether this activity was either sufficient or necessary for associative changes to occur.

Is postsynaptic activity sufficient for associative changes to occur? To examine this question, we first paired activity in one sensory neuron with a train of action potentials produced directly in the postsynaptic neuron by injecting a prolonged depolarizing current pulse in the motor neuron (see Fig. 2). Strictly speaking, Hebb's postulate requires that the paired (CS^+) neuron "takes part in firing" the postsynaptic (motor) neuron. In our experiments the CS^+ neuron produced subthreshold depolarization of the motor neuron, but firing of the motor neuron by the US did not occur until after the CS^+ stimulation was over. We chose this paradigm because it matches the paradigm that produces conditioning of the withdrawal reflex (Carew et al., 1981, 1983) and associative changes at the sensory neuron-motor neuron synapses (Hawkins et al., 1983a). By contrast, simultaneous presentation of the CS^+ and the US, which would be more consistent with a strict interpretation of Hebb's
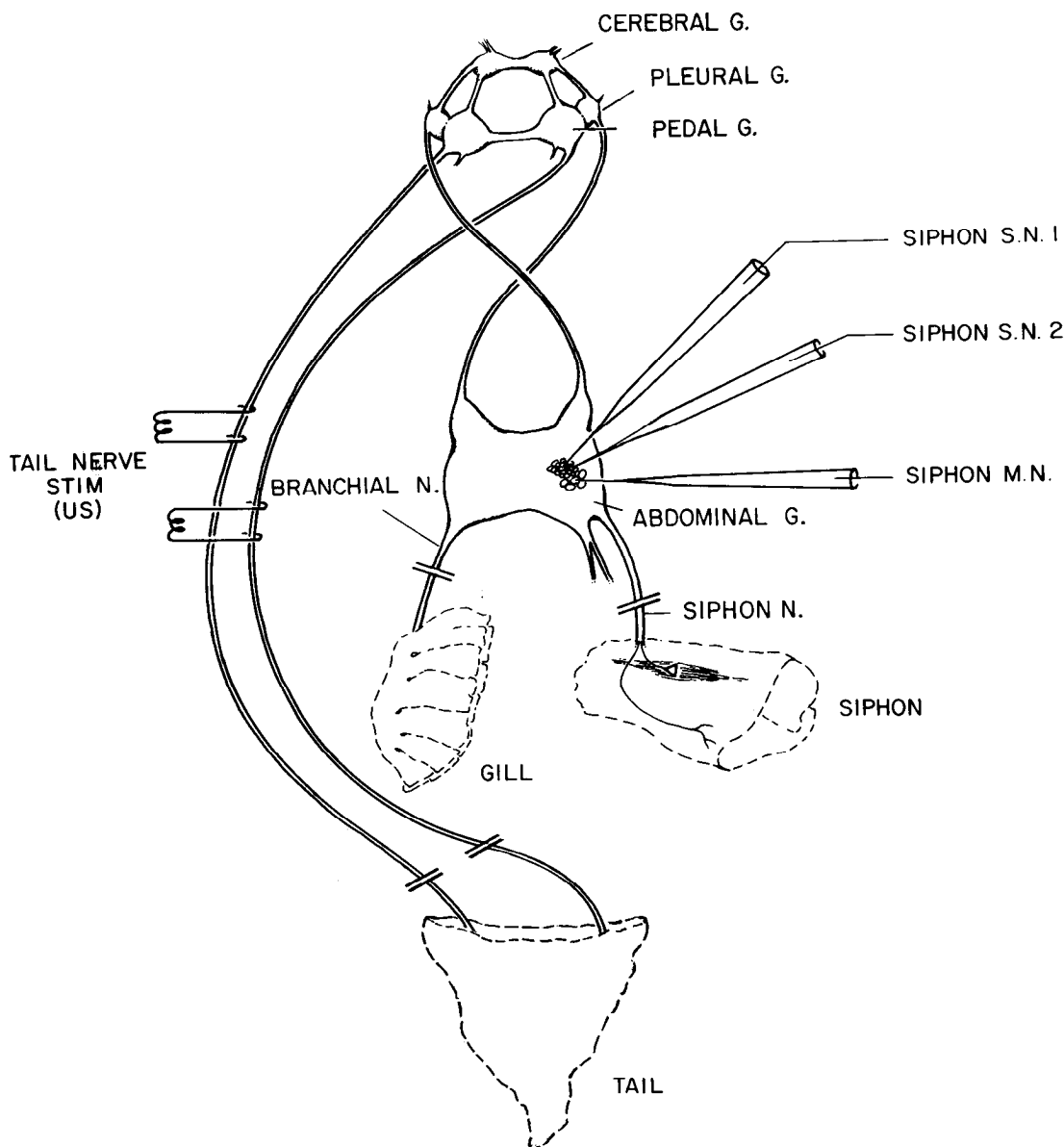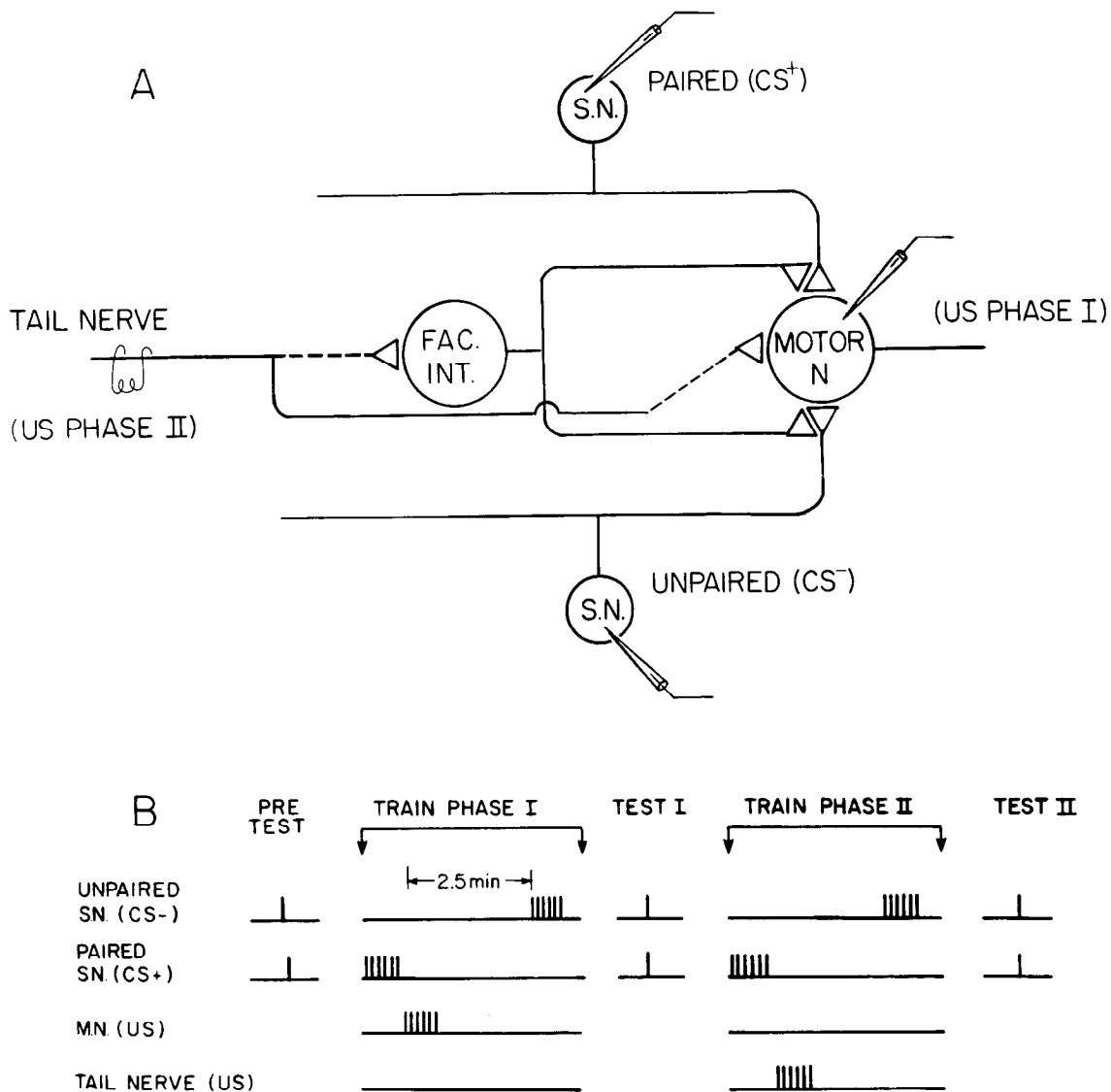
Figure 1. Schematic diagram of experimental preparation. The central nervous system of *Aplysia* was dissected free and pinned out in a Lucite recording chamber. Two siphon sensory neurons and an identified siphon motor neuron were simultaneously impaled in the abdominal ganglion: one sensory neuron served as CS$^+$, the other as CS$^-$ (see the text for details). Nerves from the tail (posterior pedal nerves) were pinned around stimulating electrodes in the chamber to provide the US input. *Dashed lines* indicate the target organs that the various nerves innervate.

postulate, does not produce good conditioning of this reflex (Hawkins et al., 1983b). Thus the central question of these experiments was whether a Hebb-type mechanism contributes to the associative changes we have observed previously in the behavior and in the synaptic connections. The number and frequency of action potentials produced in the motor neuron (about 10 to 15 spikes in 1.5 sec) were chosen to approximate the response of that neuron to tail nerve stimulation. On each of five trials, with an intertrial interval of 5 min, the paired sensory neuron was caused to fire a train of action potentials, and this was followed immediately by action potentials in the motor neuron. The other (unpaired) sensory neuron was caused to fire an identical number of action potentials 2.5 min later. This phase of the

experiment was followed by a test (test I) 15 min after training; then a second phase was run in which activity in each sensory neuron was either paired or unpaired with tail nerve stimulation (Fig. 2). Following this second training phase, a second test (test II) was performed.

An example of the results is shown in Figure 3. The EPSPs from the paired and unpaired sensory neurons were of roughly equivalent amplitudes prior to training (pretest: 8.7 mV and 8.4 mV, respectively). Following five trials with postsynaptic action potentials as the US, the EPSPs from paired and unpaired sensory neurons were both reduced in amplitude by about 45% (test I: from 8.7 to 5.0 mV and from 8.4 to 4.4 mV, respectively). Thus, both sensory neurons showed synaptic depression produced by repeated stimulation; neither showed en-

A

PAIRED (CS⁺)

S.N.

TAIL NERVE

(US PHASE Ⅱ)

FAC.
INT.

MOTOR
N

(US PHASE Ⅰ)

UNPAIRED (CS⁻)

S.N.

B

	PRE TEST	TRAIN PHASE I	TEST I	TRAIN PHASE Ⅱ	TEST Ⅱ

UNPAIRED
S.N. (CS−)

|←—2.5min—→|

PAIRED
S.N. (CS+)

M.N. (US)

TAIL NERVE (US)

Figure 2. Protocol of experiment examining the sufficiency of postsynaptic activity as a US. *A*, Diagram of experimental arrangement. Two siphon sensory neurons (*S.N.*) and a siphon motor neuron (*M.N.*) were simultaneously impaled. Stimulation of each SN produced a monosynaptic EPSP in the M.N. *B*, Diagram of protocol. In phase I of the experiment, activity in one S.N. (CS⁺) was paired with action potentials produced directly in the motor neuron with depolarizing current (US-phase I) while activity in the other S.N. (CS⁻) was specifically unpaired. In phase II, activity in the S.N.s was either paired or unpaired with tail nerve stimulation (US-phase II).

hanced synaptic transmission. However, following five more training trials in phase II, in which tail nerve stimulation was used as the US, a clear differential facilitation of the EPSP from the paired sensory neuron was observed (test II). Thus, the EPSP from the paired sensory neuron increased from 5.0 mV (test I) to 11.2 mV (test II), whereas the EPSP from the unpaired sensory neuron increased substantially less, from 4.4 mV (test I) to 5.6 mV (test II). One can directly compare the EPSPs from these paired and unpaired sensory neurons by expressing their test amplitudes as a percentage of their respective pre-training amplitudes. Thus, although EPSPs from both paired and unpaired neurons declined when postsynaptic stimulation served as the US (to 57% and 52% of pretraining amplitude, respectively), when tail nerve stimulation was used as the US, the EPSP

from the paired sensory neuron was facilitated to 128% of its pretraining amplitude, whereas the EPSP from the unpaired neuron was only 66% of its pretraining amplitude.
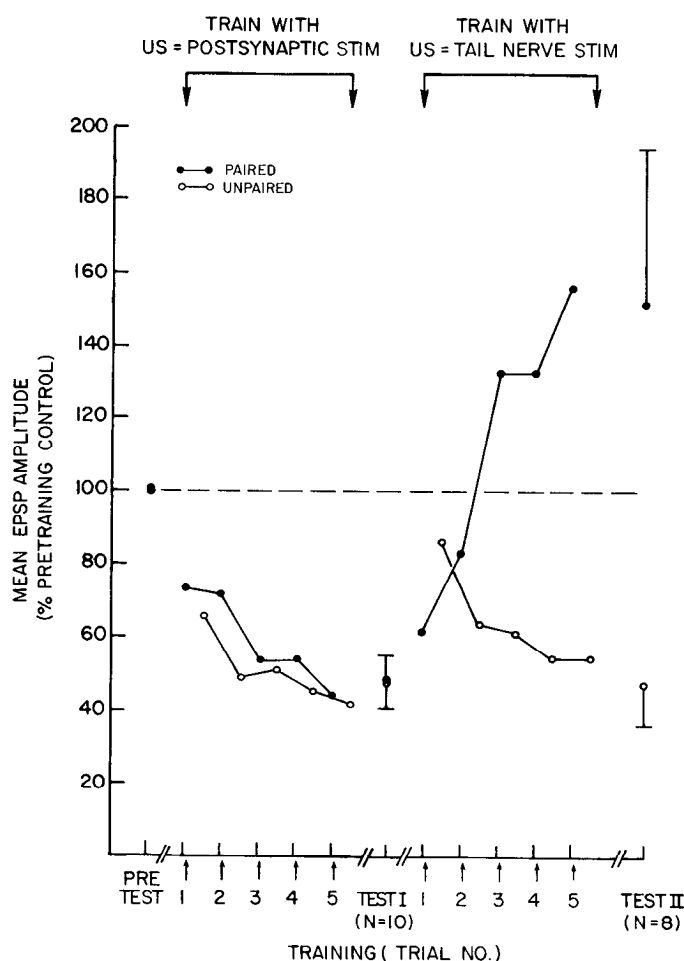
A summary of 10 experiments is shown in Figure 4. As this graph illustrates, intracellularly produced activity in the postsynaptic neuron produced no facilitation of EPSP amplitude from either the paired or unpaired sensory neurons. Rather, during the five trials in which action potentials in the postsynaptic cell served as reinforcement, both EPSPs showed progressive synaptic depression so that 15 min after training (test I), their mean amplitude was only about 50% of their pretraining control amplitude. Thus, postsynaptic activity was not sufficient to produce differential facilitation of the EPSP. By contrast, in eight experiments, when the train-
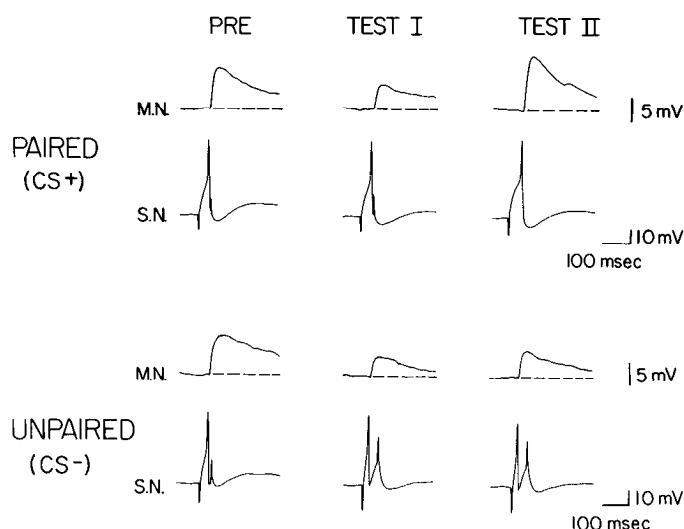
Figure 3. Results of an experiment examining the sufficiency of postsynaptic activity as a US. *PRE*, The amplitudes of the EPSPs from paired (*CS*+) and unpaired (*CS*−) sensory neurons (*S.N.*s) onto the motor neuron (*M.N.*) are approximately equal (8.75 and 8.44 mV, respectively). *TEST I*, Following five trials with motor neuron activity as a US, both EPSPs show no facilitation; rather they both show synaptic decrement (to 5.0 and 4.3 mV, respectively). TEST II, When tail nerve stimulation is used as the US, differential facilitation is produced in the paired S.N. compared to the unpaired one (11.25 mV compared to 5.62 mV; see the text and Fig. 3 for details). This experiment was carried out in artificial seawater containing 6 times normal Ca^{2+} (66 mM) and 3 times normal Mg^{2+} (165 mM) to reduce contributions of interneurons to the EPSP.

Figure 4. Summary of experiments examining the sufficiency of postsynaptic activity as a US. Training with postsynaptic stimulation as the US (*upward arrows*, phase I) produces no activity-dependent enhancement; rather, synaptic decrement is produced to about 50% of control (*dashed line*) for both paired and unpaired sensory neurons (*Test I*). In contrast, when tail nerve stimulation is used as the US (*upward arrows*, phase II), significant differential facilitation is produced (*TEST II:* $p <$ 0.025). All experiments shown in this figure as well as in Figure 5 were carried out in normal artificial seawater.

ing procedure was switched so that tail nerve stimulation served as the US, there was clear differential facilitation of the EPSPs from paired sensory neurons compared to those from unpaired sensory neurons (in 2 of the 10 experiments the impalement of one of the three nerve cells was lost during the second phase). In the 15-min test after this second phase of the experiment (test II), the EPSP from the paired neuron was significantly facilitated to a mean of 151% of its own pretraining amplitude ($t_7 = 3.52$, $p < 0.025$); by contrast, the EPSP from the unpaired neuron was only 47% of its own pretraining amplitude. Thus, at the same synapses where directly produced postsynaptic activity was ineffective as a US, stimulation of the tail nerve produced clear differential facilitation of synaptic transmission.

Is postsynaptic activity necessary for associative changes to occur? Since tail nerve stimulation resulted in brisk trains of action potentials in the siphon motor neuron, it is possible that this postsynaptic activity was necessary for the differential facilitation of the EPSPs from the paired sensory neuron observed in the previous experiment. To test this possibility, the postsynaptic siphon motor neuron was held hyperpolarized during training so that it did not fire action potentials in response to the US. As in phase II of the previous experiment, on each of the five trials (with an intertrial interval of 5 min), the sensory neuron that was chosen to be paired with the US was caused to fire a train of action potentials which was immediately followed by a train of electrical pulses to the tail nerves. The other (unpaired) sensory

neuron was caused to fire an identical number of action potentials 2.5 min later. Early in training the amplitudes of both sensory neuron EPSPs began to increase, although the EPSPs from the paired sensory neurons tended to increase more (Fig. 5). However, later in training, the EPSP from the unpaired sensory cell declined below control level, whereas the EPSP from the paired sensory neuron remained substantially above control. When tested 15 min after the last training trial, the EPSP from the paired neuron was significantly facilitated compared to its own pretraining amplitude (mean = 174.6% of pretraining control, $t_9 = 3.55$, $p < 0.025$), whereas the EPSP from the unpaired sensory neuron was not facilitated (mean = 85.9% of pretraining control).

Differential facilitation of synaptic transmission could also be assessed by comparing the difference between facilitation of EPSPs from paired and unpaired sensory neurons within the same experiment. This was done by
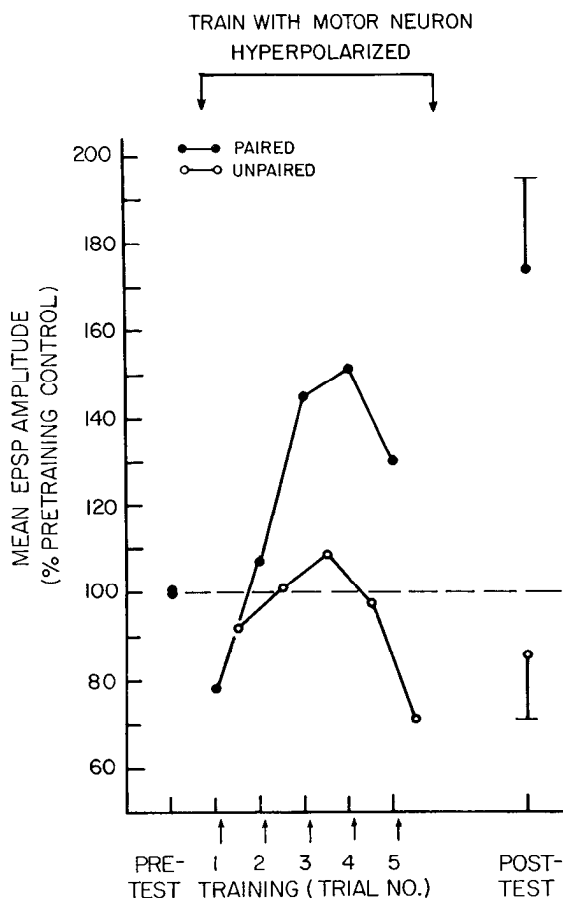
Figure 5. Summary of experiments examining the necessity of postsynaptic activity during conditioning. During training the motor neuron was hyperpolarized so that it fired no action potentials in response to the US (*upward arrows*). Nonetheless there was significant differential facilitation of the EPSPs from the paired sensory neurons compared to unpaired ($p < 0.025$).

subtracting the normalized value (test scores expressed as a percentage of prescores) for facilitation of the unpaired EPSP from the normalized value for the paired EPSP. Thus, each experiment ($N = 10$) contributed a single score reflecting the difference in facilitation of the EPSPs from paired and unpaired sensory neurons. This comparison revealed significant differential facilitation of the EPSP from the paired sensory neuron (mean difference between paired and unpaired EPSPs = 88.7%; $t_9 = 3.35$, $p < 0.025$). Since the postsynaptic neuron was held hyperpolarized and not permitted to fire during training or testing, these results indicate that postsynaptic activity is not necessary to produce temporally specific associative changes in synaptic efficacy.
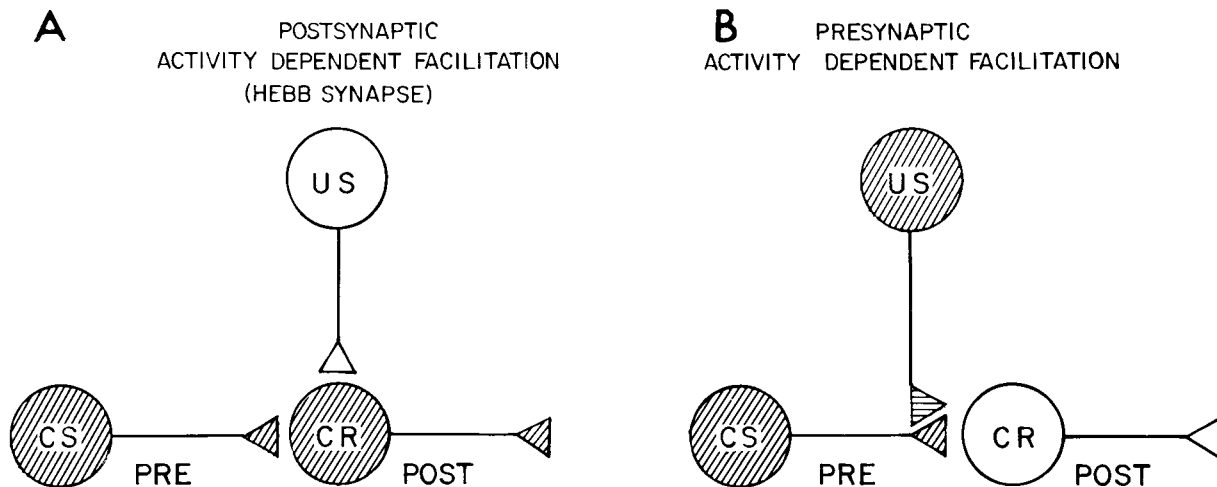
Discussion

Hebb's postulate and classical conditioning in Aplysia. We have attempted to test directly Hebb's postulate for associative learning (Hebb, 1949) by examining an identified set of synapses known to undergo associative changes that contribute to classical conditioning of the siphon and gill-withdrawal reflex in *Aplysia*. We have found that the pairing of impulse activity in the postsynaptic cell with activity in the presynaptic cell is not

critical for the production of the temporally specific change in synaptic effectiveness that accompanies the learning. Confirming previous results, we have found that pairing of activity in the presynaptic cell with facilitatory input is critical for associative changes to occur (Hawkins et al., 1983a).

Hebb's postulate and the model we have proposed based on our results nonetheless share three important features. (*1*) Both models emphasize that learning involves a change in efficacy of previously existing synaptic connections. (*2*) Both emphasize that associative learning need not require special neuronal circuitry since the mechanism of temporal specificity can reside in individual neurons. (*3*) Both emphasize that neuronal activity per se plays an essential role in the cellular mechanisms underlying the formation of temporal associations. The principal difference between the two models centers upon *which neurons* must be active to give rise to the associative change. Hebb proposed that learning might require coincident activity in both the presynaptic and postsynaptic cell, and he suggested that activity in one cell, the postsynaptic cell (such as might be caused by the US), would be critical for plastic changes in another cell, the presynaptic neuron (see Fig. 6A). Our data indicate that only the cell undergoing the plastic change need be active in association with activity in the US pathway. Thus, in our system, where the plastic change occurs presynaptically, presynaptic activity, coincident with activation of the US pathway, is critical for temporally specific synaptic facilitation (Fig. 6B). An attractive feature of this model is that it provides a mechanism for the temporal specificity of associative learning which is simple, involving only an amplification, in an activity-dependent way, of the same cellular process (presynaptic facilitation) that underlies sensitization.[3]

Activity-dependent modulation of the K^+ channel could produce changes in postsynaptic as well as presynaptic properties. In the model we have proposed, the mechanism for the associative learning involves changes in the release of transmitter from the sensory neurons (Hawkins et al., 1983a). Thus, activity-dependent enhancement of presynaptic facilitation involves a change in the way one neuron *transmits* information to other cells. However, this should not be taken to imply that associative learning might not also change postsynaptic or *receptive* properties such as the input resistance or threshold for spike initiation. We have found that the facilitation of synaptic transmission during conditioning involves a

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[3] We have focused on the synapses between the sensory (CS) neurons and the motor (CR) neurons of the siphon withdrawal reflex, since alterations in transmission at these synapses will influence the reflex response that we measure during conditioning. We have no information as to whether other synapses in *Aplysia* show Hebb-type plasticity. For example, the question could be raised whether the synapses between the facilitator (US) neurons and the sensory (CS) neurons might have Hebb-type properties, since our training procedure also involves paired spike activity in those neurons (Fig. 6B). While we have not studied these synapses, we know that the facilitators do not take part in firing the sensory neurons during our training procedure, since spike activity in the facilitators *follows* spike activity in the sensory neurons. Thus, Hebb-type plasticity at these synapses (if it exists) could not contribute to the associative changes we observe.

A   POSTSYNAPTIC
ACTIVITY DEPENDENT FACILITATION
(HEBB SYNAPSE)

B   PRESYNAPTIC
ACTIVITY DEPENDENT FACILITATION

Figure 6. Comparison of postsynaptic and presynaptic models. *A,* Hebb postulated that postsynaptic (*CR*) activity is essential in conjunction with presynaptic (*CS*) activity, for an increase in synaptic strength. *B,* Our model hypothesizes that presynaptic (*CS*) activity, paired with facilitator (*US*) activity, is critical for a temporally specific increase in synaptic strength (see the text for details). *Shading* indicates that activity is essential.

decrease in K^+ conductance in the presynaptic sensory neurons which increases transmitter release by broadening the action potential (Hawkins et al., 1983a). This reduction in K^+ current also causes an increase in input resistance and a decrease in threshold for spike initiation in the sensory neurons (Klein and Kandel, 1980). Thus, if a similar change in a K^+ conductance occurred in an interneuron or a motorneuron, in addition to facilitating transmitter release from the terminals of that neuron, it would also increase the efficacy of excitatory synaptic input to that cell (Carew and Kandel, 1976; Schulman and Weight, 1976; Klein and Kandel, 1980; Walters and Byrne, 1983). This modification of these postsynaptic properties would in turn be enhanced by pairing spike activity in the postsynaptic cell with the US input in the same way that presynaptic facilitation is enhanced and thus could contribute to associative learning (for evidence that this type of mechanism may occur in a vertebrate, see Woody et al., 1978). Thus, the critical finding in *Aplysia* is that only the cell undergoing the plastic change need be active in coincidence with the US pathway for associative learning to occur.

Cases in which receptive (postsynaptic) properties of neurons were modulated would superficially resemble a Hebb-type mechanism, because activity in the postsynaptic cell would be critical to produce the change. However, such cases would not require that presynaptic activity be coincident with postsynaptic activity as Hebb suggested, but would rather require that the postsynaptic action potentials be temporally paired with facilitatory input. Moreover, this type of plasticity would occur at many synapses onto a cell and not be restricted, as Hebb's postulate would predict, only to the synapses that were activated by the CS input.

In conclusion, although our evidence indicates that Hebb's postulate does not account for classical conditioning of the defensive withdrawal reflex in *Aplysia*, our results should not be taken to imply that a mechanism such as that proposed by Hebb might not underlie or contribute to other instances of learning. Associative

learning is being studied on the cellular level in several invertebrate and vertebrate preparations (Cohen, 1974; Woolacott and Hoyle, 1977; Davis and Gillette, 1978; Woody et al., 1978; Alkon, 1980; Chang and Gelperin, 1980; Crow and Alkon, 1980; Hoyle, 1980; Sahley et al., 1981; Tsukahara et al., 1981; Alkon et al., 1982; Ito, 1982; McCormick et al., 1982; Walters and Byrne, 1983). It will be of interest to see whether activity-dependent plasticity has a role in learning in these preparations.

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