Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 2577–2581, April 1984
Neurobiology

Branch-specific heterosynaptic facilitation in *Aplysia* siphon sensory cells

(presynaptic facilitation/post-tetanic potentiation/neuronal plasticity/sensitization/classical conditioning)

GREGORY A. CLARK AND ERIC R. KANDEL

Center for Neurobiology and Behavior, Departments of Physiology and Psychiatry, Columbia University, College of Physicians and Surgeons, and New York State Psychiatric Institute, New York, NY 10032

Contributed by Eric R. Kandel, January 9, 1984

ABSTRACT ***Aplysia* siphon sensory cells exhibit heterosynaptic facilitation of transmitter release during both sensitization and classical conditioning of the siphon withdrawal response. In the present study, we asked whether facilitation must invariably enhance transmission at all terminals of a neuron or whether facilitation can instead occur at one set of terminals without also occurring at other terminals of the same cell. To examine this question, we compared effects of local application of serotonin and of connective stimulation on transmission at central and peripheral branches of single sensory cells. We found that heterosynaptic facilitation can be branch-specific and can occur at either central or peripheral synapses independently. We also found that siphon sensory cells exhibit homosynaptic post-tetanic potentiation, allowing us to compare effects of hetero- and homosynaptic facilitation in the same cells. By contrast to heterosynaptic facilitation, homosynaptic facilitation occurs concomitantly at both central and peripheral synapses of siphon sensory cells. Thus, while both heterosynaptic and homosynaptic facilitation involve increases in transmitter release from sensory neuron terminals, heterosynaptic facilitation provides a greater specificity and flexibility in the modification of synaptic connections.**

Both sensitization (1–3) and classical conditioning (4–6) of the siphon withdrawal response in *Aplysia* involve heterosynaptic facilitation of transmitter release from LE siphon sensory cells onto central siphon motor neurons (refs. 7–10; see ref. 11 for review). In these two learning situations, a noxious stimulus to another part of the body, such as the tail, activates a group of facilitator interneurons (12, 13) that initiate a cAMP-dependent phosphorylation cascade underlying facilitation in the sensory cells (9, 14–16). Comparable facilitation can also be produced by electrical stimulation of the pleuroabdominal connectives (which carry input from the tail) (3, 7) and by application of serotonin, a putative transmitter of some facilitator interneurons (9, 10, 14, 16). Since similar molecular processes appear to underlie sensitization and classical conditioning in *Drosophila* (17–19) as well as facilitation in other sensory neurons in *Aplysia* (20, 21), these mechanisms may be fairly general.

With the conditions used in previous studies, heterosynaptic facilitation was found to produce changes in the excitability of the cell body (unpublished data) and to enhance transmission from sensory neuron terminals onto a number of central targets. But must heterosynaptic facilitation necessarily be cell-wide, so that it leads invariably to enhanced transmission at *all* terminals of a neuron? Or is it possible to enhance transmission at terminals onto one set of postsynaptic targets—one set of motor neurons, for example—without causing corresponding facilitation at terminals onto other target cells? Because branch-specific facilitation would enhance only selected outputs of a given cell, it would provide a high degree of specificity in the modification of neural pathways and, consequently, in the modification of behavior. For these reasons, branch-specific features have been proposed on theoretical grounds and incorporated into a number of conceptual models of plasticity in neural networks (22, 23). To date, however, there has been no attempt to explore this possibility experimentally.

The siphon sensory cells of *Aplysia* offer an advantageous model system for investigating branch-specific facilitation. As shown in Fig. 1, the siphon sensory cells synapse not only onto central siphon motor neurons and interneurons in the abdominal ganglion, but also onto a set of peripheral siphon motor neurons located at the distal end of the siphon nerve, several centimeters away (24). The physical separation of the two terminal regions maximizes the possibility of identifying regional facilitatory effects. It also allows the central and peripheral neuropils to be manipulated independently with pharmacological agents. In the present study, we compare effects of localized application of serotonin and activation of facilitator interneurons on transmission at central and peripheral synapses of individual sensory neurons. We find that it is possible to facilitate transmission at either central or peripheral terminals independently.

A preliminary report of these results has appeared (25).

METHODS

Aplysia californica weighing 80–200 g were commercially obtained. Animals were anesthetized by injection of isotonic $MgCl_2$ (approximately one-half to one times the body weight) into the hemocoel, and dissections were performed in a mixture of equal parts of artificial seawater and $MgCl_2$. Abdominal ganglia were dissected from the animals together with the attached pleuroabdominal connectives and siphon nerve, and were pinned to the Sylgard floor of a recording chamber. The connective tissue sheath covering the abdominal ganglion was then partially removed. In most experiments that involved recording from peripheral motor neurons, the distal end of the siphon nerve was treated with 0.1% bovine trypsin (Sigma, type XI; EC 3.4.21.4) for 5 min at room temperature (19–23°C) to soften the sheath. To terminate trypsin action, the nerve was subsequently rinsed several times with 1% trypsin inhibitor (Sigma, type II-S) and then bathed in trypsin inhibitor for 10 min before the artificial seawater was replaced.

To facilitate the measurement of monosynaptic excitatory postsynaptic potentials (EPSPs) evoked by stimulation of sensory neurons, all experiments were conducted in artificial seawater containing elevated concentrations of Mg^{2+} and Ca^{2+} [composition, in mM: NaCl, 338; KCl, 10; $CaCl_2$, 50; $MgCl_2$, 100; $NaHCO_3$, 2.5; Tris·HCl buffer (pH 7.6), 10]. Neurons were impaled with single-barreled glass microelec-

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: EPSP, excitatory postsynaptic potential; PTP, post-tetanic potentiation.

trodes (10–20 MΩ) filled with 2.5 M KCl, and standard intracellular stimulation and recording techniques were used. LE siphon sensory cells were identified by morphological and electrophysiological characteristics (3, 26). Postsynaptic targets included central siphon motor neurons and interneurons located on the rostral edge of the LE cluster (unpublished data) and, in some cases, peripheral siphon motor neurons located at the distal end of the siphon nerve (24). In these cases, the two sets of postsynaptic targets were isolated from each other by threading the siphon nerve through a slit in a plastic wall that divided the recording chamber in two; the slit was then sealed with Vaseline, allowing the central and peripheral neuropils to be perfused independently (Fig. 1). Sensory and motor neurons were then sampled until a sensory neuron that projected to both a central and peripheral target was located. Cells were obtained in which the EPSPs evoked in central and peripheral followers were of approximately equal amplitudes (central EPSP amplitude equaled 6.5 ± 0.7 mV; peripheral EPSP amplitude equaled 10.0 ± 1.5 mV, $n = 40$; all data expressed as mean ± SEM). Similarly, both central and peripheral followers were hyperpolarized by the same amount (usually 10–20 mV) to prevent spiking. After a sensory cell with the appropriate targets had been isolated, the sensory neuron was rested for at least 15 min before beginning the experiment to allow recovery from any synaptic depression that may have occurred during the initial testing (2, 3, 27). For experiments involving serotonin, serotinin creatine sulfate (Sigma) was dissolved in artificial seawater to a concentration of 0.1 mM and added to the central or peripheral recording chamber through the perfusion lines. All experiments were conducted at room temperature.

RESULTS

Siphon Sensory Cells Exhibit Branch-Specific Facilitation in Response to Local Application of Serotonin. To test for branch-specific facilitation, we first compared effects of localized serotonin application on central and peripheral synapses of individual sensory neurons. Action potentials were elicited by intracellular stimulation of the sensory neuron once every 40 sec, and the EPSPs elicited in a central and peripheral follower were recorded. In addition, the input resistance of the central and peripheral followers was monitored at the end of each trial with constant current hyperpolarizing pulses (0.25–1.0 nA). Following 10 trials, 0.1 mM serotonin was applied briefly (10–20 sec) onto either the central or peripheral nervous system and was washed out while testing continued (3–4 bath vol per min). After 10 more trials, 0.1 mM serotonin was applied onto the other nervous system, so that effects of serotonin were tested on both central and peripheral synapses in each preparation ($n = 14$). Experiments were counterbalanced so that serotonin was applied centrally first in seven preparations and peripherally first in the other seven preparations. Percent facilitation was measured by comparing the amplitudes of the EPSPs elicited in the four trials before and the four trials after serotonin application.

We found that facilitation can occur at either central or peripheral synapses independently (Fig. 2). Application of serotonin onto the central neuropil caused a marked facilitation of EPSPs in central followers, while the concomitantly

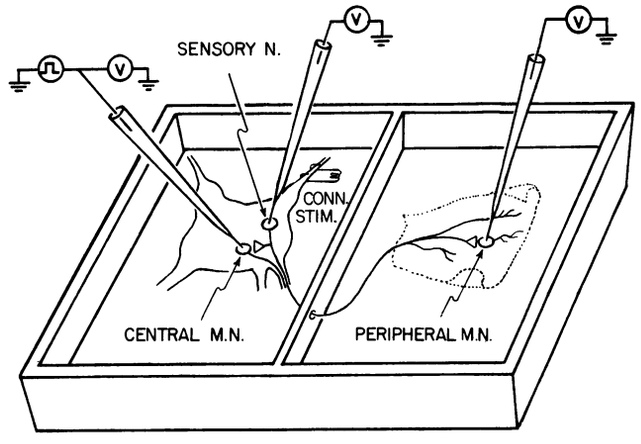

FIG. 1. Experimental arrangement for examining branch-specific facilitation in siphon sensory cells. Monosynaptic EPSPs evoked by stimulation of a single siphon sensory cell were recorded in one central siphon motor neuron or interneuron (located nearby in the abdominal ganglion) and in one peripheral motor neuron (located at the distal end of the siphon nerve in the siphon skin). For illustrative purposes, the siphon is depicted (dashed lines), though it was not included in actual experiments. Central and peripheral nervous systems were perfused independently, allowing serotonin to be applied to either one or the other. Stimulation of the pleuroabdominal connective could also be administered through a pair of stimulating posts. N., neuron; M.N., motor neuron; CONN. STIM., connective stimulation.

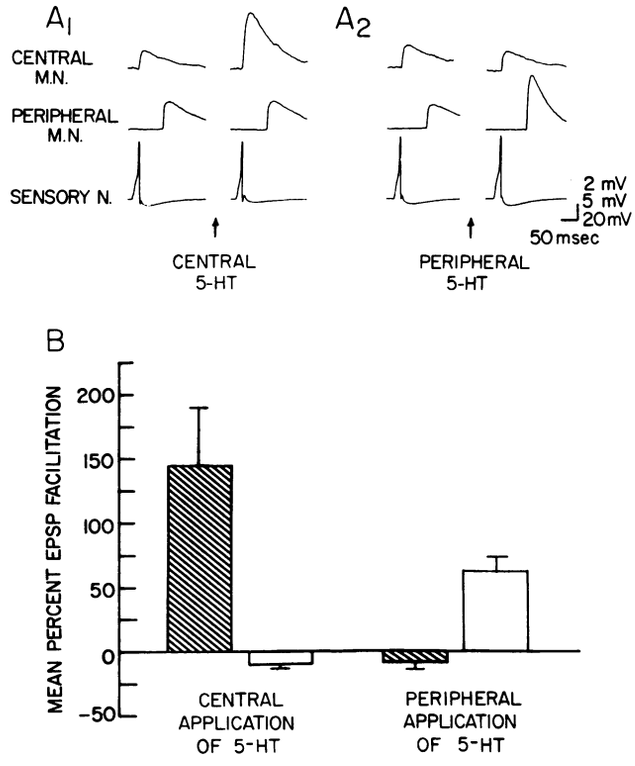

FIG. 2. Siphon sensory cells exhibit branch-specific facilitation. Experimental arrangement as in Fig. 1. (*A*) Example of branch-specific facilitation produced by localized application of serotonin (5-HT). EPSPs evoked by stimulation of a siphon sensory cell (bottom trace) were recorded in a central and peripheral siphon motor neuron (top and middle traces, respectively). (A_1) EPSPs evoked before (left) and after (right) application of 5-HT onto the central nervous system. (A_2) EPSPs evoked before (left) and after (right) application of 5-HT onto the peripheral nervous system. Same preparation as in A_1. Application of 5-HT onto the central nervous system enhanced central but not peripheral EPSPs, while application of 5-HT onto the peripheral nervous system enhanced peripheral but not central EPSPs. (*B*) Group data demonstrating that localized application of 5-HT can produce branch-specific facilitation ($n = 14$). ▨ and □, EPSPs recorded in central followers and peripheral followers, respectively. Left half: effect of 5-HT applied to the central nervous system. Right half: effect of 5-HT applied to the peripheral nervous system. Facilitation was measured by comparing the size of the EPSPs in the four trials before and the four trials after 5-HT application. Zero percent facilitation indicates no change.

recorded peripheral EPSPs showed slight synaptic depression (2, 3, 27) from repeated stimulation of the sensory neuron (143% ± 45% increase vs. 10% ± 3% decrease, $P < 0.01$, t test for related means). Similarly, application of serotonin onto the peripheral nervous system facilitated peripheral but not central EPSPs (62% ± 15% increase vs. 9% ± 6% decrease, $P < 0.01$). Although serotonin tended to cause somewhat greater central than peripheral facilitation, this difference was not significant. We do not know whether this tendency was due to a slight difference in responsivity in the two sets of terminals or was instead due to other factors, such as access of serotonin to the neuropil. Serotonin also caused a small decrease in the input resistance of both central followers (9% ± 3% decrease, $P < 0.01$, $n = 13$) when applied centrally and peripheral followers (18% ± 3% decrease, $P < 0.001$, $n = 12$) when applied peripherally (in some preparations bridge imbalance precluded measurement of input resistance). This finding is consistent with other lines of evidence, including quantal analyses and biochemical assays of sensory neurons, which have demonstrated that heterosynaptic facilitation is a presynaptic phenomenon (3, 7, 8, 10, 14, 16).

Stimulation of the Pleuroabdominal Connective Causes Branch-Specific Facilitation. The above findings indicate that the intracellular mechanisms underlying heterosynaptic facilitation are sufficiently discrete to allow branch-specific modifications. Nonetheless, this capacity is not necessarily sufficient to indicate whether branch-specific facilitation can actually occur under natural conditions. For example, if all facilitator interneurons projected uniformly to all terminals of a sensory neuron, then one might expect all of the terminals to show comparable facilitation. In contrast, if some interneurons projected to only one set of terminals, but not the other, then activation of these interneurons should produce branch-specific facilitation.

To assess this possibility, we examined effects of stimulation of the left pleuroabdominal connective on EPSPs recorded from central and peripheral followers. Previous experiments have shown that connective stimulation antidromically activates the L29 cells, a group of facilitator interneurons that enhance transmission at synapses onto central followers. Although there may well be other facilitator interneurons that have not been identified, the L29 cells do not project out the siphon nerve (12, 13). We therefore hypothesized that connective shock would enhance central EPSPs without causing corresponding facilitation at peripheral synapses. As shown in Fig. 3, such was in fact the case. EPSPs elicited by stimulation of a siphon sensory cell (once every 40 sec) were recorded for 10 trials before and after stimulation of the left connective ($n = 18$). Connective shock (6 Hz for 4 sec, using 1-msec, 15-V pulses across a pair of 1-mm, 20-gauge silver wire stimulating posts) caused a dramatic increase in the amplitude of central EPSPs (182% ± 50%, $P < 0.01$) but little or no increase in the amplitude of peripheral EPSPs (7% ± 16% increase, not significant). The difference between central and peripheral facilitation was highly significant ($P < 0.001$). Moreover, when tested 10 trials later, peripheral EPSPs showed a 78% ± 18% increase in response to serotonin ($P < 0.001$), indicating peripheral synapses were capable of facilitation. Connective shock also caused a slight increase in the input resistance of central followers (13% ± 2%, $P < 0.001$, $n = 17$) but not peripheral followers (2% ± 3% increase, not significant, $n = 18$). These findings corroborate the results of serotonin application and indicate that natural facilitators can also cause branch-specific facilitation.

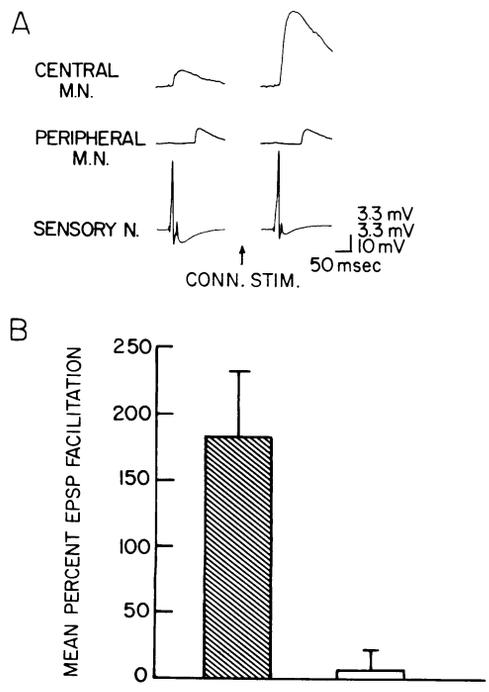

FIG. 3. Stimulation of the left abdominal can cause branch-specific facilitation. Experimental arrangement as in Fig. 1. (*A*) Example of EPSPs evoked before (left) and after (right) stimulation of the left connective. Traces as in Fig. 2*A*. (*B*) Group data demonstrating branch-specific facilitation produced by connective stimulation ($n = 18$). Graphics and computations as in Fig. 2*B*. ▨ and □, EPSPs recorded in central followers and peripheral followers, respectively.

Post-Tetanic Potentiation (PTP) Occurs in Siphon Sensory Cells but Exhibits Little Spatial Specificity. Because heterosynaptic facilitation is mediated by a second messenger whose distribution may be spatially limited (see *Discussion*), it can occur at different branches independently. Is this also true for other forms of plasticity? For homosynaptic forms of facilitation such as PTP, enhancement arises from activity within the neuron itself. As a consequence, one might expect homosynaptic facilitation to exhibit relatively little specificity or flexibility in the the site of modification.

To compare effects of hetero- and homosynaptic facilitation in siphon sensory cells, it was first necessary to establish that LE siphon sensory cells could in fact exhibit PTP that was not confounded by heterosynaptic mechanisms. With this in mind, we recorded from two siphon sensory cells and a single central siphon motor neuron to which they both projected. Each sensory cell was stimulated alternately (once per min for each cell) to establish a baseline for the monosynaptic EPSPs evoked in the motor neuron. After five trials, one sensory cell was stimulated rapidly (6 Hz, 4 sec, yielding 26 ± 4 spikes), while the control sensory cell was not stimulated. EPSPs were then tested for five more trials. Percent facilitation was measured by comparing amplitudes of the EPSPs in the two trials before and the two trials after the tetanizing train. High-frequency stimulation invariably enhanced the EPSPs evoked by the stimulated cell, while EPSPs evoked by the control cell showed only ongoing synaptic depression (2, 3, 27) from the repeated testing (96% ± 14% increase vs. 21% ± 7% decrease, $n = 8$, $P < 0.001$). At the end of 5 min, EPSPs elicited by the tetanized cell were still significantly facilitated compared to controls (39% ± 17% increase vs. 24% ± 9% decrease, $P < 0.05$). These results suggest that the observed facilitation was in fact homosynaptic and not due to recruitment of facilitator interneurons during the high-frequency discharge of the sensory neuron.

Because PTP is believed to be due to the accumulation of Ca^{2+} that occurs during the invasion of the action potential burst into terminal regions (28–30), we reasoned that PTP, unlike heterosynaptic facilitation, should occur concomi-

tantly at both central and peripheral terminals of the siphon sensory cells. To test this hypothesis, we conducted an experiment similar to the one described above but, in this case, recorded from a single sensory neuron that projected to both a central and a peripheral follower. As before, EPSPs were tested once per min for five trials; the sensory neuron was then driven with a high-frequency train (6 Hz, 4 sec, yielding 24 ± 1 spikes) and EPSPs were tested for five more trials. Results (Fig. 4) showed that PTP occurred equally at both central and peripheral terminals (131% ± 27% increase, $P < 0.01$, and 124% ± 36% increase, $P < 0.02$, respectively, $n = 8$, no significant differences between central and peripheral facilitation).

DISCUSSION

Heterosynaptic Facilitation Can Be Branch-Specific. Results of both localized serotonin application as well as activation of endogenous facilitator interneurons indicate that *Aplysia* siphon sensory cells can exhibit branch-specific facilitation. While we have not yet found a group of facilitator interneurons that can selectively facilitate peripheral synapses or that can cause greater facilitation than that observed following connective shock, the fact that serotonin can selectively facilitate transmission at peripheral synapses suggests that in principle such an effect could occur.

One possible explanation for the specificity observed following connective shock is that there are at least some facilitator interneurons that project to central but not peripheral synaptic regions of the siphon sensory cells. The fact that the L29 cells, a group of interneurons that has been shown to cause heterosynpatic facilitation at central synapses, do not project out the siphon nerve lends support to this interpretation (12, 13). Other explanations are possible, however. For example, projections of facilitator interneurons may simply diminish quantitatively in the periphery, particularly in finer branches of the distal siphon nerve and thereby cause less peripheral than central facilitation. It is also possible that peripheral projections of facilitators are more susceptible to damage during the dissection procedure. However, even in such cases, the marked difference in central and peripheral heterosynaptic facilitation indicates that sensory neurons have the biological capacity for branch-specific facilitation.

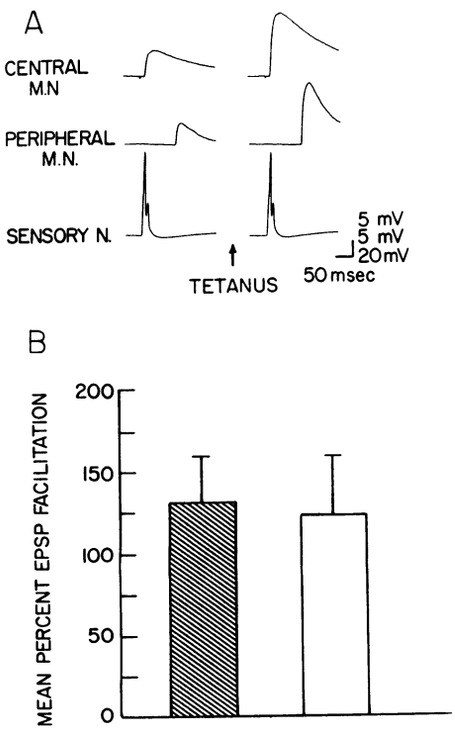

FIG. 4. PTP occurs at both central and peripheral synapses of siphon sensory cells. Experimental arrangement as in Fig. 1. (*A*) EPSPs evoked in a central and peripheral siphon motor neuron (top and middle traces) by a siphon sensory cell (bottom trace) before (left) and after (right) high-frequency stimulation of the sensory cell. Note that both central and peripheral EPSPs are potentiated. (*B*) Comparison of EPSP facilitation at central synapses (▨) and peripheral synapses (□) following high-frequency stimulation of siphon sensory cells ($n = 8$).

PTP in Siphon Sensory Cells Exhibits Little Spatial Specificity. The present studies also demonstrate that siphon sensory cells can exhibit PTP. Along similar lines, Walters and Byrne have previously documented PTP in tail sensory neurons in *Aplysia* (20, 31, 32) and have also recently observed PTP in LE siphon sensory cells (32). The only previous evidence for homosynaptic facilitation in siphon sensory cells was an enhancement of recovery from synaptic depression at stimulation of 1 Hz (33). The finding of PTP in siphon sensory cells is of interest because these cells also exhibit a number of other forms of plasticity and because they have a known behavioral function.

The effects of PTP also provide an interesting contrast to those of heterosynaptic facilitation. Because the signal for PTP—neuronal activity—invades both processes, PTP occurs concomitantly at both central and peripheral branches of siphon sensory cells. In some systems, different synapses of a neuron have been shown to exhibit different amounts of homosynaptic plasticity (24, 34–37). However, in these cases, the differences appear to be due to differences in the properties of the two sets of terminals and seem relatively invariant. In contrast, heterosynaptic facilitation depends not only on the properties of the terminal regions but also on the innervation patterns of extrinsic facilitating inputs. As a consequence, heterosynaptic facilitation can occur independently at different terminal regions that have no apparent intrinsic differences and are each capable of facilitation.

How Does Branch-Specific Facilitation Work? Heterosynaptic facilitation in siphon sensory cells involves a cAMP-dependent phosphorylation of a serotonin-sensitive K^+ channel or one or more proteins closely associated with it. Phosphorylation closes the channel and thereby prolongs the duration of the action potential and enhances transmitter release (8–10, 14–16). Because the breakdown of cAMP is relatively rapid and its intracellular distribution relatively slow, this mechanism appears well-suited for the types of subcellular modifications involved in branch-specific facilitation. In support of this interpretation, Castellucci *et al.* (38) have recently found that when the adenylate cyclase that synthesizes cAMP is inactivated (via intracellular injection of guanosine 5′-[β-thio]diphosphate), facilitatory effects in sensory neurons decay rapidly, with a half-life of ≈30 sec, indicating that cAMP is rapidly degraded. In contrast, intracellular distribution of cAMP appears to be extremely slow over long distances. While no precise data are available, Koike and Nagata (39) have shown that diffusion of acetylcholine injected into *Aplysia* neurons requires >24 hr to reach levels only 0.1% of the initial concentration at distances of 4 cm or more (the distance between central and peripheral synapses). Thus, a facilitatory input that contacts a sensory neuron on only some of its branches will initially elevate cAMP in those and not others. Although some cAMP may diffuse out of facilitated branches, its concentration will diminish with time and distance, resulting in lower levels (and correspondingly less facilitation) in more distant terminals.

Although this interpretation appears to account for the results of the present study, several questions remain. While we have shown that heterosynaptic facilitation can be specific for terminals located relatively far apart (4–6 cm), we do not yet know whether such specificity can occur between two synapses that are relatively closely spaced. Similarly,

we have examined here only short-term heterosynaptic facilitation and do not know whether long-term heterosynaptic facilitation can also be branch-specific.

Branch-Specific Facilitation Is a Candidate Mechanism for Behavioral Response Specificity. Because branch-specific facilitation provides a high degree of specificity in the modification of neural pathways, it is a potentially important property that may underlie a wide variety of neural and behavioral phenomena. We pose here one example in the context of our own work to illustrate the types of advantages that branch-specific effects may be able to confer.

In many instances of classical conditioning, the conditioned training stimulus can come to elicit a variety of different conditioned motor responses depending on the nature of the reinforcing stimulus—e.g., pairing tone presentations with eye shock produces conditioned eyelid responses in the rabbit (40), while pairing tone presentations with leg shock produces conditioned leg flexion (41). As yet, there is no evidence that *Aplysia* exhibits this type of behavioral response specificity or what the underlying mechanism might be. However, because branch-specific facilitation can enhance only selected outputs of the siphon sensory cells onto particular motor neurons, it provides a potential mechanism for conditioning one group of motor responses without affecting others. Clearly, a number of other mechanisms—e.g., changes in selected motor neurons or interneurons—could also contribute to response specificity. Nonetheless, because activity-dependent enhancement of heterosynaptic facilitation in siphon sensory cells appears to provide the stimulus and temporal specificity that characterize classical conditioning of the siphon withdrawal response (5, 6), it may be possible to account for all three types of specificity with a single cellular mechanism.

We thank Drs. T. Abrams, R. Hawkins, I. Kupfermann, J. Byrne, and E. Walters for comments on an earlier version of the manuscript and V. Castellucci and W. Frost for help throughout. We also thank K. Hilten and L. Katz for preparation of the figures. This work was supported by National Institute of Mental Health Grant MH08859 to G.A.C. and by National Institutes of Health Program Project Award GM32099, National Institute of Mental Health Research Scientist Award MH8558, and Office of Naval Research Grant N00014-83-K-0166 to E.R.K.

1. Pinsker, H., Kupfermann, I., Castellucci, V. & Kandel, E. R. (1970) *Science* **167,** 1740–1742.
2. Kupfermann, I., Castellucci, V., Pinsker, H. & Kandel, E. R. (1970) *Science* **167,** 1743–1745.
3. Castellucci, V., Pinsker, H., Kupfermann, I. & Kandel, E. R. (1970) *Science* **167,** 1745–1748.
4. Carew, T. J., Walters, E. T. & Kandel, E. R. (1981) *J. Neurosci.* **1,** 1426–1437.
5. Carew, T. J., Hawkins, R. D. & Kandel, E. R. (1983) *Science* **219,** 397–400.
6. Hawkins, R. D., Abrams, T. W., Carew, T. J. & Kandel, E. R. (1983) *Science* **219,** 400–405.
7. Castellucci, V. & Kandel, E. R. *Science* **194,** 1176–1178.
8. Klein, M. & Kandel, E. R. (1980) *Proc. Natl. Acad. Sci. USA* **77,** 7492–7496.
9. Klein, M., Camardo, J. S. & Kandel, E. R. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 5713–5717.
10. Siegelbaum, S., Camardo, J. S. & Kandel, E. R. (1982) *Nature (London)* **299,** 413–417.
11. Kandel, E. R. & Schwartz, J. H. (1982) *Science* **218,** 433–443.
12. Hawkins, R. D., Castellucci, V. F. & Kandel, E. R. (1981) *J. Neurophysiol.* **45,** 304–314.
13. Hawkins, R. D., Castellucci, V. F. & Kandel, E. R. (1981) *J. Neurophysiol.* **45,** 315–326.
14. Brunelli, M., Castellucci, V. & Kandel, E. R. (1976) *Science* **194,** 1178–1181.
15. Castellucci, V. F., Nairn, A., Greengard, P., Schwartz, J. H. & Kandel, E. R. (1982) *J. Neurosci.* **2,** 1673–1681.
16. Bernier, L., Castellucci, V. F., Kandel, E. R. & Schwartz, J. H. (1982) *J. Neurosci.* **2,** 1682–1691.
17. Dudai, Y. & Quinn, Q. G. (1980) *Trends Neurosci.* **3,** 28–30.
18. Dudai, Y., Jan, Y. N., Byers, D., Quinn, W. G. & Benzer, S. (1976) *Proc. Natl. Acad Sci. USA* **73,** 1684–1688.
19. Byers, D., Davis, R. L. & Kiger, J. A. (1981) *Nature (London)* **289,** 79–81.
20. Walters, E. T. & Byrne, J. H. (1983) *Science* **219,** 405–408.
21. Ocorr, K. A., Walters, E. T. & Byrne, J. H. (1983) *Soc. Neurosci. Abstr.* **9,** 169.
22. Hebb, D. O. (1949) *Organization of Behavior* (Wiley, New York).
23. Marr, D. (1969) *J. Physiol. (London)* **202,** 437–470.
24. Bailey, C. H., Castellucci, V. F., Koester, J. & Kandel, E. R. (1979) *J. Neurophysiol.* **42,** 530–557.
25. Clark, G. A. (1983) *Soc. Neurosci. Abstr.* **9,** 915.
26. Byrne, J., Castellucci, V. & Kandel, E. R. (1974) *J. Neurophysiol.* **37,** 1041–1064.
27. Castellucci, V. F. & Kandel, E. R. (1974) *Proc. Natl. Acad. Sci. USA* **71,** 5004–5008.
28. Katz, B. & Miledi, R. (1965) *Proc. R. Soc. London Ser. B.* **161,** 496–503.
29. Rahaminoff, R. (1968) *J. Physiol. (London)* **195,** 471–480.
30. Kretz, R., Shapiro, E. & Kandel, E. R. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 5430–5434.
31. Walters, E. T. & Byrne, J. H. (1982) *Soc. Neurosci. Abstr.* **8,** 386.
32. Walters, E. T. & Byrne, J. H. (1984) *Brain Res.* **293,** 377–380.
33. Byrne, J. H. (1982) *J. Neurophysiol.* **48,** 431–438.
34. Bittner, G. D. (1968) *J. Gen. Physiol.* **51,** 731–758.
35. Atwood, H. L. (1967) *Nature (London)* **215,** 57–58.
36. Frank, E. (1973) *J. Physiol. (London)* **233,** 635–658.
37. Muller, K. J. & Nicholls, J. G. (1974) *J. Physiol. (London)* **238,** 357–369.
38. Castellucci, V. F., Bernier, L., Schwartz, J. H. & Kandel, E. R. (1983) *Soc. Neurosci. Abstr.* **9,** 169.
39. Koike, H. & Nagata, Y. (1979) *J. Physiol. (London)* **295,** 397–417.
40. Gormezano, I., Schneiderman, N., Deaux, E. & Fuentes, I. (1962) *Science* **138,** 33–34.
41. Donegan, N. H., Lowery, R. W. & Thompson, R. F. (1983) *Soc. Neurosci. Abstr.* **9,** 331.