Proc. Natl. Acad. Sci. USA
Vol. 83, pp. 7994–7998, October 1986
Neurobiology

Facilitatory transmitters and cAMP can modulate accommodation as well as transmitter release in *Aplysia* sensory neurons: Evidence for parallel processing in a single cell

(K^+ currents/second messengers/presynaptic facilitation/excitability/sensitization)

MARC KLEIN, BINYAMIN HOCHNER*, AND ERIC R. KANDEL

Howard Hughes Medical Institute, Center for Neurobiology and Behavior, Departments of Pharmacology and Physiology, Columbia University College of Physicians and Surgeons; and The New York State Psychiatric Institute, New York, NY 10032

Contributed by Eric R. Kandel, July 7, 1986

ABSTRACT **Presynaptic facilitation of transmission from sensory to motor neurons contributes significantly to behavioral sensitization of defensive withdrawal reflexes in *Aplysia*. Presynaptic facilitation is associated with a decrease in the serotonin-sensitive K^+ conductance. This decrease broadens the presynaptic action potential. In addition, the procedures that cause facilitation—stimulation of the connective (the pathway from the tail and head), application of modulatory transmitters, or injection of cAMP—also increase the excitability of the sensory neurons as tested with intracellular depolarizing pulses injected into the cell body. The increased excitability is reflected in a decreased threshold for generating action potentials and a reduction in accommodation to prolonged constant current stimuli. By influencing the excitability of the peripheral processes of the sensory neurons, stimulation of the connectives or serotonin also produces a small enhancement of the response of the sensory neurons to a tactile stimulus applied to the siphon. The excitability changes appear to result, at least in part, from the same cellular mechanisms that lead to broadening of the action potential, a cAMP-mediated closure of K^+ channels. Therefore, these findings indicate that the same class of mechanisms can, in principle, have a dual action and provide further evidence for parallel processing in the modulation of transmitter release from a single neuron.**

In several behavioral systems, sensitization and classical conditioning have been shown to involve heterosynaptic facilitation of preexisting neuronal connections by activity in a modulatory pathway (1–6). Based on these studies, two major classes of heterosynaptic facilitatory actions have been described: (*i*) a presynaptic change that leads to an increase in the amount of transmitter released by each action potential (4–7) and (*ii*) a change, often described in postsynaptic cells, that results in an increase in the firing rate of the cell (3). Here we address the question of how these two facilitatory actions are related. Can they occur in parallel, within a single neuron? If so, do they reflect two different mechanisms, or two aspects of a common mechanism?

In the initial analysis of the biophysical mechanisms of sensitization in *Aplysia*, Klein and Kandel (8) focused on the monosynaptic component of this reflex. They found that the heterosynaptic (presynaptic) facilitation of the connections between the sensory and motor neurons produced by serotonin (5-HT) and other facilitatory transmitters was associated with a decrease in a 5-HT-sensitive K^+ current called S current (9–11). Reduction of this K^+ current produces broadening of the action potential that enhances transmitter release on the one hand, and, on the other hand, is accompanied by an increase in firing elicited by a depolarizing current step injected into the cell body (8, 9, 12). Similar changes have been found to underlie sensitization of the tail-withdrawal reflex in *Aplysia* (4) and classical conditioning of both gill- and tail-withdrawal reflexes (5, 6).

Depression of K^+ currents also accompanies the heterosynaptic facilitation associated with classical conditioning in *Hermissenda* (13). In *Hermissenda*, the depression of K^+ currents, perhaps also produced by the facilitatory transmitter 5-HT (14, 15), leads to an increase in firing rate in the type B photoreceptor (3). Moreover, depression of K^+ current by modulatory transmitters is not limited to invertebrates; the excitability increase produced by acetylcholine and norepinephrine in cortical neurons is also caused by closure of one or another species of K^+ channel (16, 17).

We show here that in *Aplysia* the same apparent cellular mechanism—transmitter-mediated closure of K^+ channels by cAMP-dependent protein phosphorylation—can influence both the transmitter-releasing capabilities of a neuron and its firing rate. By closing K^+ channels, modulatory transmitters and cAMP (the cytoplasmic messenger for these transmitters) enhance the duration of the presynaptic action potential and increase transmitter release (8, 9, 11). In addition, the S channel conductance, which is active at rest and increases modestly in a time-dependent manner with depolarization (9), acts as both a hyperpolarizing force and a shunt of excitation in the sensory neurons. Consequently, a reduction of the S channel conductance can also lead (perhaps in conjunction with the modulation of other channels) to a decrease in threshold for spike initiation (8) and increased firing (anti-accommodation) during prolonged stimuli.

Our findings suggest that the two consequences of K^+ channel closure can occur separately or together, depending on the site of action of the modulatory neuronal input. Modulation on or near the presynaptic terminals can regulate the amount of transmitter released by a single action potential; modulation near a spike trigger zone can change the neuron's tendency for accommodation.

METHODS

Abdominal ganglia were removed from *Aplysia californica* (Sea Life Supply, Pacific Biomarine), desheathed, and pinned to Sylgard for stimulation and recording. In experiments where peripheral tactile stimulation was used, the siphon skin and part of the mantle shelf connected to the ganglion by the siphon nerve were also removed from the animal and pinned out in another part of a Sylgard chamber (18). Tactile stimuli were applied with a solenoid-driven probe (19); nerves were stimulated by using suction elec-

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: 5-HT, serotonin; SCP_B, small cardioactive peptide B.

*Present address: Department of Neurobiology, Life Sciences Institute, Hebrew University, Jerusalem, Israel.

trodes (6 Hz for 5–20 sec). Intracellular stimulation and recording were carried out by conventional techniques.

Artificial seawater containing 460 mM NaCl, 10 mM KCl, 55 mM $MgCl_2$, 11 mM $CaCl_2$, and 10 mM Hepes (Sigma) was buffered to pH 7.6. Serotonin creatinine sulfate (5-HT; Sigma) and small cardioactive peptide B (SCP_B; Peninsula Laboratories, San Carlos, CA) were dissolved in artificial seawater and diluted 1:100 in the bath, usually to final concentrations of 100 and 10 μM, respectively. Sodium salts of cAMP and 5'-AMP (Sigma) were dissolved in distilled water to 0.1 M. Responses of sensory neurons to depolarizing pulses were tested before, during, and after impalement with micropipettes containing these nucleotide solutions; the nucleotides entered the cells by diffusion. All experiments were carried out at room temperature.

RESULTS

Stimulating a sensitizing nerve pathway and exposing the sensory neurons of the abdominal ganglion to one of three facilitating transmitters (5-HT, SCP_B, and the unidentified transmitter released by cell L29) have a common action: closure of a novel K^+ channel, the S channel. Closure of S channels results from transmitter-activated cAMP-dependent protein phosphorylation (20) and contributes to sensitization of the gill and siphon withdrawal reflex by broadening the action potential and enhancing transmitter release from the terminals of the sensory neurons (9). Similar actions have been found in the sensory neurons of the tail that mediate sensitization of tail withdrawal (21, 22).

In earlier studies we have observed that stimulating the connectives from the head or tail and applying 5-HT produce a second action; they enhance the firing of the sensory neurons (8, 9). To examine this change in firing behavior more closely, we first tested the excitability of the soma of the sensory neuron with intracellularly injected depolarizing current. We then also explored the cellular distribution of these changes in excitability by applying tactile stimuli to the neuron's receptive field in the siphon skin.

Modulatory Transmitters and cAMP Have an Anti-accommodative Effect on the Response of Sensory Neurons to Long Current Pulses. A brief 5- to 50-msec suprathreshold depolarizing-current pulse injected into a sensory neuron in the abdominal ganglion usually produces one or two action potentials. Stimulation of a modulatory pathway from the head or tail (the left or right pleuro abdominal connective) or application of 5-HT broadens the action potential by ≈10% in the abdominal ganglion (9) and 20% in the pleural ganglion (22, 23). These procedures do not increase the number of spikes produced by these short pulses (Fig. 1*A*), although they can lower the firing threshold and shorten the spike latency.

Long depolarizing current pulses (500 msec or more in duration; 0.4–2.3 nA) usually produce a brief burst of action potentials in the sensory neurons followed by accommodation of firing. Connective stimulation changes this firing pattern markedly, so that the neuron now fires throughout the duration of the depolarization (Fig. 1*B*). In 11 experiments, the average number of spikes increased 6-fold from 1.14 ± 0.78 to 6.65 ± 2.68 (mean ± SD, $P < 0.01$). In addition, the firing latency for the first spike was shortened by 30% (from 37.37 ± 18.29 to 27.50 ± 9.92 msec, $n = 10$, $P < 0.01$). When just subthreshold current pulses were used, facilitating stimuli could cause the cell to fire at a lower level of depolarizing current ($n = 4$) (Fig. 1*C*).

The 5-HT-sensitive K^+ current is active at the resting level, increases moderately with depolarization to a new steady state, and is relatively noninactivating (9). Depression of a K^+ current such as the S current could account for, or at least contribute to, the anti-accommodative actions and changes in excitability. To determine whether depression of the S current, which is responsible for the broadening of action potentials, might also contribute to the changes in firing, we examined the effects of three agents known to close the S channels: 5-HT, SCP_B, and intracellular cyclic AMP (8–12).

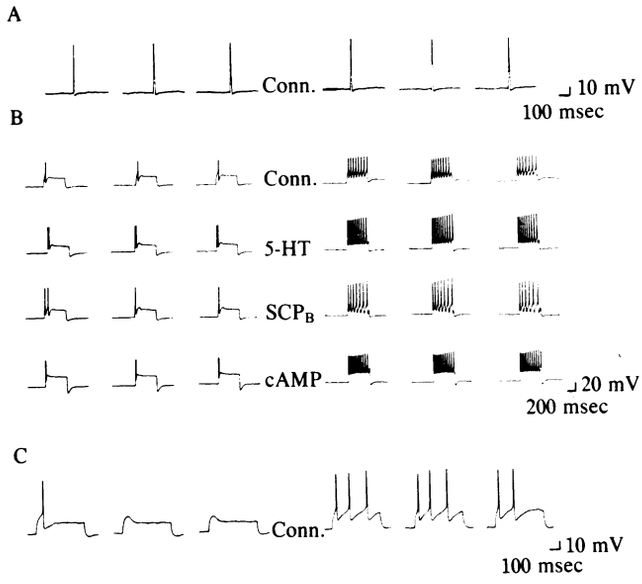

FIG. 1. Effects of modulatory stimuli on central excitability of sensory neurons. (*A*) Connective stimulation (Conn.) does not modulate spike number with short intracellular depolarizing pulses. A sensory neuron was fired once every 30 sec with a 5-msec intracellular depolarizing pulse before and after connective stimulation. In this and all subsequent records, the action potentials are attenuated by the limited frequency response of the chart recorder. (*B*) Long pulses reveal an increase in central excitability induced by connective stimulation, bath application of serotonin (5-HT) or small cardioactive peptide (SCP_B), or intracellular injection of cAMP. Five-hundred-millisecond depolarizing steps were applied to sensory neuron somata with an intracellular microelectrode once every 30 sec. (*C*) Connective stimulation also lowers spike threshold. Long, constant-current depolarizations of the somatic membrane that straddled firing threshold are shown prior to and after connective stimulation. After connective stimulation, the pulses exceeded threshold.

Using long constant-current depolarizing pulses to elicit firing of a sensory neuron, we found that application of 5-HT caused a 4-fold increase in the number of spikes (from 1 to 4 ± 2.94) (Fig. 1*B*). The small (11 amino acid) peptide SCP_B also increased the number of spikes in the train from 1.5 ± 0.24 to 8.33 ± 2.35 spikes (Fig. 1*B*). Similarly, cAMP injected into the cell body increased firing in every one of eight experiments (Fig. 1*B*). On average, the number of spikes more than doubled, increasing from 5 ± 2.93 in the control condition to 13.5 ± 3.59 after impaling the cell with a cAMP-filled micropipette. After withdrawal of the cAMP pipette from the cell, the number of spikes declined to 5.38 ± 4.72. In contrast, there was no change in the number of spikes in the three experiments in which we impaled cells with micropipettes filled with 5'-AMP (the breakdown product of cAMP). The subsequent insertion of a cAMP micropipette into two of these cells caused an increase from 3 to 6 spikes in one case, and from 4 to 14 in the other. Thus, procedures that close the 5-HT-sensitive K^+ channel also produce an increase in firing.

These increases in firing may result from the increase in membrane resistance caused by these facilitatory treatments and not an action on accommodation *per se*. To examine this possibility, we recorded the number of spikes elicited with depolarizing currents of different magnitudes before and after either 5-HT application or cAMP injection. We found that in

many cases no matter how much depolarizing current was injected, the firing of the sensory neuron was limited to a few spikes at the beginning of the prolonged depolarization. After 5-HT or cAMP application, there was spiking throughout the duration of the current step (Fig. 2; see also ref. 24). This finding suggests that these agents do not increase firing by simply increasing the input resistance of the cell and thereby the voltage across the membrane, but they specifically counteract membrane processes that contribute to accommodation in these cells.

Modulatory Transmitters Have Only a Slight Anti-accommodative Effect on the Response of Sensory Neurons to Long Tactile Stimuli. Sensory neurons *in vivo*, however, are not normally activated by inputs to the cell body but by tactile stimulation of the siphon skin. Does modulation of excitability occur when sensory neurons are excited by natural stimuli? To answer this question, we tested the effects of nerve stimulation on firing generated by tactile stimuli to the siphon. As with intracellularly generated action potentials, we found that the number of spikes elicited with short (50 msec) stimuli was not changed by connective stimulation (Fig. 3*A*). With long stimuli (500 msec), we found a marginal increase in excitability. Firing increased in 4 of 10 experiments and did not change in the other 6. The average increase was 30% when averaged over all of the experiments (from 3.85 ± 2.37 to 5 ± 3.63; $P < 0.05$, one-tailed t test) and 60% (from 4.75 ± 2.66 to 7.63 ± 4.03) when only experiments that showed an increase were considered.

A change in spike number was not, however, the only result of stimulating the connectives. Even though the total number of spikes did not increase, stimulation of the connective often resulted in a change in the *pattern* of firing in response to tactile stimulation of the skin. This change took two forms: first, there was sometimes a shift in the firing pattern, so that spikes were clustered near the onset of the response to the tactile stimulus (Fig. 3*B1*). Second, there was sometimes an enhanced off-response to the tactile stimulus (Fig. 3*B2*). Thus, when tactile stimuli to the siphon are used,

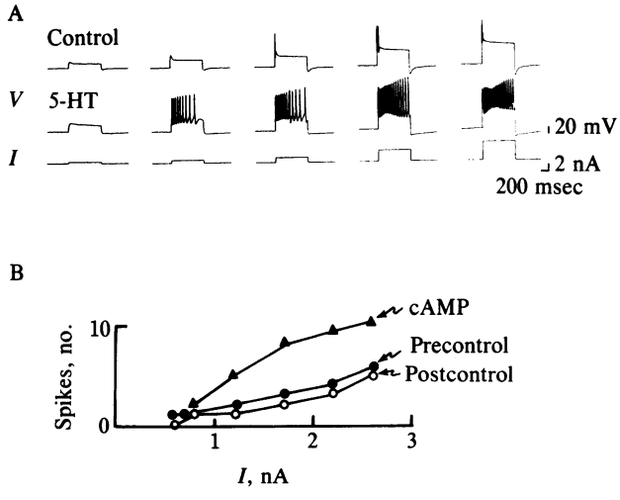

FIG. 2. Reduction of accommodation by 5-HT and cAMP. (*A*) A series of 1-sec depolarizing current pulses was injected into a sensory neuron before (control) and after (5-HT) application of 50 μM 5-HT. The interpulse interval was 10 sec. The marked accommodation that occurs in the control is greatly reduced by 5-HT, even where the depolarization in the presence of 5-HT is less than that in the control (compare the second and third 5-HT records to the fourth and fifth control records, for example). (*B*) Reduction of accommodation by cAMP. The number of spikes elicited by 500-msec depolarizing-current steps is plotted as a function of current magnitude before, during, and after cAMP injection. As is the case with 5-HT, cAMP reduces the accommodation to these pulses.

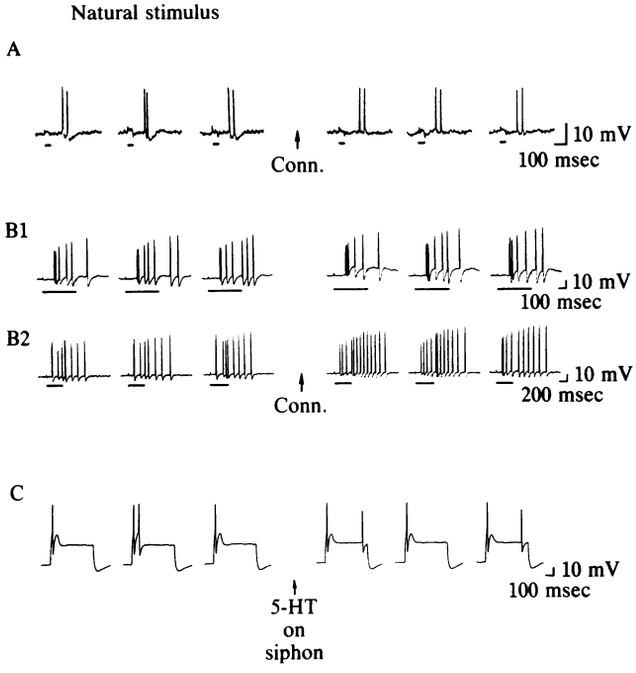

FIG. 3. Effects of connective stimulation (Conn.) on peripheral excitability of sensory neurons. (*A*) Responses to tactile stimuli of short duration are not modulated by connective stimulation. A 50-msec tactile stimulus to the siphon (bar) elicited two spikes both before and after nerve stimulation. The reduction in the hyperpolarizing afterpotentials is an indication that the nerve stimulation was effective in reducing somatic K^+ current. (*B1*) The number of spikes elicited by a 500-msec tap was not increased by connective stimulation, but spike frequency at the beginning of the response was enhanced. The increased depolarizing afterpotentials are presumably a result of modulation of conductance in the soma membrane and might contribute to an increase in spiking in some cases. (*B2*) A 500-msec tap to the siphon elicited 8 or 9 spikes before nerve stimulation and 10–13 spikes afterwards. The increase in this case was largely due to an increase in a delayed response to the tap. (*C*) Evidence for an increase in peripheral excitability can be detected in the cell body. Intracellular depolarizing pulses in the cell body elicit an additional, reflected spike after application of 5-HT to the siphon. Reflected spikes are also sometimes seen after connective stimulation but are often obscured by the increased firing in the soma.

sensitizing stimulation affects primarily the transmitter release caused by each action potential; there is only a small and unreliable effect on the number and pattern of action potentials.

Response of the Sensory Neurons to Local Application of 5-HT. Although stimulation of the connective had only a small effect on peripheral excitability, the question arises: How is it achieved? This question is of particular interest because neurons may have receptors to 5-HT and other modulatory transmitters on their sensory-transducing endings.

It is conceivable that connective stimulation increases the response to a tactile stimulus by enhancing central excitability, so that the same number of action potentials propagating in from the periphery might give rise to more action potentials at a central trigger zone. We tested this possibility by applying 5-HT (100 μM) only to the abdominal ganglion and examining the response to a tactile stimulus applied to the siphon. We saw the usual increase in spike number to an intracellular step but no increase in the number of spikes elicited by the tactile stimulus (1.55 ± 0.53 spikes to 1.35 ± 0.47 spikes; $n = 4$, $P > 0.1$). These results indicate that a change in central excitability alone is not enough to account for the enhancement of the response to a tactile stimulus by

connective stimulation. There must be a change in the periphery.

The possibility that modulatory cells also act on the sensory neurons in the periphery has been explored in other contexts. The sensory neurons make synaptic contacts not only within the abdominal ganglion, on the central gill and siphon motor neurons, but also peripherally, with peripheral siphon motor neurons (25). Paralleling our findings on excitability, Clark and Kandel (26) found significant facilitation by connective stimulation at central sensory-to-motor connections within the abdominal ganglion and found only marginal facilitation at sensory synapses with the peripheral motor neurons on the siphon nerve. Nonetheless, the synapses in the siphon nerve could be greatly facilitated by bath-applied 5-HT, indicating that the peripheral processes of the sensory neurons have both the receptors to 5-HT and the molecular machinery necessary for facilitation. Therefore, we repeated the experiment of Clark and Kandel, now looking at the effects of 5-HT applied to the siphon on the response to a tactile stimulus. We found that local application of 5-HT to the siphon caused an increase in the number of spikes propagating to the cell body (from 2.52 ± 1.73 to 4.05 ± 2.32; $n = 4$, $P < 0.025$) without causing any change in the number of spikes generated centrally by an intracellular depolarizing pulse.

That modulation of the response to tactile stimulation is the result of a direct action on sensory neuron processes rather than an increase in tension or some other change in mechanical properties at the siphon is suggested by the finding that, although 5-HT applied directly to the siphon causes no change in central excitability, it occasionally causes a reflected spike in response to a central depolarization (Fig. 3*C*). Such spikes differ from those that are usually initiated centrally in that they rise abruptly from the baseline without being preceded by any noticeable slowly rising depolarization. Similar reflected spikes appear after nerve stimulation as well. Since we rarely saw spikes generated in this way without the siphon being attached to the ganglion, they most likely propagated into the ganglion from the siphon. The possibility that connective stimulation can increase the probability of a spike being generated in the periphery in the absence of a tactile stimulus implies that, in addition to acting on their cell bodies and synaptic terminals (7, 27, 28), the processes of the modulatory neurons might also end on and modulate the excitability of mechanoreceptor processes of the sensory neurons in the siphon skin. Finally, it is also possible that circulating levels of modulatory substances such as 5-HT may change during sensitization and that both central and peripheral receptors are activated by these substances.

DISCUSSION

Multiple Consequences of K^+-Current Modulation. We have presented initial evidence to indicate that accommodation in firing shown by sensory neurons may be caused at least in part by an increase in the S current during the course of a depolarizing step (9), much as is the case with the M and the AHP current in sympathetic neurons (29). The S current is present at the resting level, increases moderately with depolarization, is nonactivating, and is the major current modulated by 5-HT (9). Moreover, all of the procedures that reduce the S current—stimulation of the connectives, application of modulatory transmitters (5-HT and SCP_B), or intracellular injection of cAMP—cause a marked reduction in accommodation.

However, our experiments do not allow us to determine whether this anti-accommodative effect is due only to reduction in S current. The present experiments were done under constant-current rather than constant-voltage conditions, and the currents flowing as a result of action potential firing might not be strictly comparable to those revealed under voltage clamp. It is thus possible that activation or suppression of conductances other than that of the S channel also contributes to the anti-accommodative effect of modulatory stimuli (30).

But independent of its precise quantitative role, our results indicate that, in addition to facilitating synaptic transmission by broadening action potentials, cAMP-dependent closure of K^+ channels by 5-HT (and other modulatory transmitters) also can contribute to an increase in the excitability of the sensory neurons. This finding is of particular interest because it generalizes the functional significance of a single class of cellular mechanism and suggests that in other neuronal systems, the same mechanism could act presynaptically, postsynaptically, or both, to enhance the consequences of synaptic action.

Presynaptically, this mechanism could have several effects. First, by broadening the action potential, each action potential will release more transmitter. Second, closure of K^+ channels also causes a steady-state depolarization that is likely to increase the resting Ca^{2+} current and thereby enhance transmitter release further (31). Third, by counteracting accommodation, closure of K^+ channels also might increase the number of spikes elicited by a long tactile stimulus.

Postsynaptically, closure of K^+ channels would increase the number of action potentials produced by a given synaptic potential, both because of the increase in membrane resistance and because of the decrease in accommodation. Indeed, even synaptic potentials that previously were subthreshold could now become capable of firing the cell. In parts of the neuron where the safety factor for action potential conduction is low, decreasing the threshold could increase the number of action potentials generated over the whole of the neuronal tree (32).

Increases in excitability that appear to result from modulation of K^+ conductances have now been reported in a variety of contexts and in both pre- and postsynaptic cells: sympathetic neurons (29), facial nucleus (33), and hippocampus (34), among others. In guinea pig myenteric plexus, 5-HT has been proposed to regulate gating of transmission of impulses through the cell body by reducing Ca^{2+}-dependent K^+ conductance (32).

Modulation of K^+ conductances appears to be particularly important for various forms of behavioral plasticity. In addition to *Aplysia*, where modulation of the S current plays a presynaptic role both in short-term sensitization and classical conditioning, neurons in *Hermissenda* (13) and perhaps in locust as well (35, 36) also show changes in their properties with classical conditioning that result from closure of K^+ channels. In *Hermissenda*, where the analysis is detailed, conditioning has been shown to reduce both the early and Ca^{2+}-dependent K^+ currents (13). Even in vertebrates, work on conditioning of the eye-blink response has suggested that a concomitant increase in neuronal excitability may be a causal factor in this learning paradigm, although it is as yet unknown whether K^+ channel modulation plays a role (37, 38).

Parallel Processing of Synaptic Plasticity Within Single Sensory Neurons. Earlier anatomical and physiological evidence indicates that modulatory neurons act not only on the central processes and synaptic varicosities of the sensory neuron but also on its cell body (7, 27, 28). Although we cannot completely exclude a change in mechanical properties, our results suggest that the sensory neurons have receptors to 5-HT near the peripheral receptor terminations in the siphon skin and that modulatory neurons could exert a modest action there. Thus, the present studies and those of Clark and Kandel (26) and Belardetti *et al.* (23) indicate that

the sensory neurons have the molecular machinery (the receptor, the G proteins, the cyclase and cAMP-dependent protein kinase, and various substrate proteins) necessary for modulation at several sites: in the cell body, in central and peripheral branches, and in growth cones.

The demonstration that 5-HT and other facilitatory transmitters increase the excitability of the sensory neurons and the duration of each action potential provide support for the idea (39) that short-term neuronal plasticity initiated by the cAMP-dependent protein kinase involves a broad, coordinated cellular program. Consistent with the finding of a coordinated program is the fact that, in addition to closing S channels, 5-HT has other actions that may contribute to its capability for enhancing synaptic transmission. These actions include altered handling of Ca^{2+} (39), translocation of the phospholipid-dependent C kinase (40), and enhancement of the availability of transmitter for release (41).

Just as there are multiple sites of plasticity within a single neuron, the neural pathway of the gill withdrawal reflex as a whole can be modulated at several loci (42). In addition to changes in sensory neurons, there are coordinated changes in certain interneurons and in one subclass of siphon motor cell. Thus, in the broadest sense, the finding of a molecular program for plasticity within the single neuron is perhaps the simplest instance of a general principle emerging in the cellular study of learning in this reflex: the existence of parallel processing allows memory to have multiple representations, with each of the different intracellular and cellular loci concerned with a different aspect of the representation of memory in short-term and perhaps even in long-term storage. Just as sensory and motor systems show parallel processing and multiple representation that are concerned with the analysis and reconstruction of the sensory information and motor command, so might the multiple representation of various forms of memory allow for a more elaborate reconstruction of past experience. In addition, while some of the components of short-term memory in this system might be primarily concerned with the immediate consequences of recent experience, others might be involved more in bridging from short- to long-term memory.

We thank Drs. T. Abrams, V. Castellucci, G. Clark, J. Koester, and I. Kupfermann for comments on an earlier manuscript; H. Ayers and A. Krawetz for typing the manuscript; and L. Katz and K. Hilten for preparing the figures.

1. Kandel, E. R. & Tauc, L. (1965) *J. Physiol. (London)* **181,** 1–27.
2. Castellucci, V., Pinsker, H., Kupfermann, I. & Kandel, E. R. (1970) *Science* **167,** 1745–1748.
3. Crow, T. J. & Alkon, D. L. (1980) *Science* **209,** 412–414.
4. Walters, E. T., Byrne, J. H., Carew, T. J. & Kandel, E. R. (1983) *J. Neurophysiol.* **50,** 1543–1559.
5. Hawkins, R. D., Abrams, T. W., Carew, T. J. & Kandel, E. R. (1983) *Science* **219,** 400–415.
6. Walters, E. T. & Byrne, J. H. (1983) *Science* **219,** 405–408.
7. Castellucci, V. & Kandel, E. R. (1976) *Science* **194,** 1176–1178.
8. Klein, M. & Kandel, E. R. (1978) *Proc. Natl. Acad. Sci. USA* **75,** 3512–3516.
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. Abrams, T. W., Castellucci, V. F., Camardo, J. S., Kandel, E. R. & Lloyd, P. E. (1984) *Proc. Natl. Acad. Sci. USA* **81,** 7956–7960.
12. Klein, M. & Kandel, E. R. (1980) *Proc. Natl. Acad. Sci. USA* **77,** 7492–7496.
13. Farley, J. & Alkon, D. L. (1983) *Soc. Neurosci. Abstr.* **9,** 167.
14. Crow, T. & Forrester, J. (1986) *Proc. Natl. Acad. Sci. USA*, in press.
15. Farley, J. & Auerbach, S. (1986) *Nature (London)* **319,** 220–223.
16. Adams, P. (1982) *Trends NeuroSci.* **5,** 116–119.
17. Nicoll, R. A. (1982) *Trends NeuroSci.* **5,** 369–374.
18. Byrne, J., Castellucci, V. & Kandel, E. R. (1974) *J. Neurophysiol.* **37,** 1041–1064.
19. Carew, T. J., Castellucci, V. F., Byrne, J. H. & Kandel, E. R. (1979) *J. Neurophysiol.* **42,** 497–509.
20. Shuster, J. J., Camardo, J. S., Siegelbaum, S. A. & Kandel, E. R. (1985) *Nature (London)* **313,** 392–395.
21. Walsh, J. P. & Byrne, J. H. (1983) *Soc. Neurosci. Abstr.* **9,** 458.
22. Pollock, J. D., Bernier, L. & Camardo, J. S. (1985) *J. Neurosci.* **5,** 1862–1871.
23. Belardetti, F., Schacher, S., Kandel, E. R. & Siegelbaum, S. A. (1986) in *Molecular Aspects of Neurobiology*, eds. Levi-Montalcini, R., Calissano, P., Kandel, E. R. & Maggi, A. (Springer, Berlin), pp. 15–18.
24. Dale, N., Kandel, E. R. & Schacher, S. (1986) *Soc. Neurosci. Abstr.* **12,** 1339.
25. Bailey, C. H., Castellucci, V. F., Koester, J. & Kandel, E. R. (1979) *J. Neurophysiol.* **42,** 530–557.
26. Clark, G. A. & Kandel, E. R. (1984) *Proc. Natl. Acad. Sci. USA* **81,** 2577–2581.
27. Bailey, C. H., Hawkins, R. D., Chen, M. C. & Kandel, E. R. (1981) *J. Neurophysiol.* **45,** 340–360.
28. Kistler, H. B., Jr., Hawkins, R. D., Koester, J., Steinbusch, H. W. M., Kandel, E. R. & Schwartz, J. H. (1985) *J. Neurosci.* **5,** 72–80.
29. Adams, R. P. & Galvan, M. (1986) *Adv. Neurol.* **44,** 137–170.
30. Walsh, J. P. & Byrne, J. H. (1985) *Soc. Neurosci. Abstr.* **11,** 789.
31. Shapiro, E., Castellucci, V. F. & Kandel, E. R. (1980) *Proc. Natl. Acad. Sci. USA* **77,** 629–633.
32. Grafe, P., Mayer, C. J. & Wood, J. D. (1980) *J. Neurophysiol.* **305,** 235–248.
33. VanderMaelen, C. P. & Aghajanian, G. K. (1980) *Nature (London)* **287,** 346–347.
34. Madison, D. V. & Nicoll, R. A. (1982) *Nature (London)* **299,** 636–638.
35. Woolacott, M. H. & Hoyle, G. (1976) *Soc. Neurosci. Abstr.* **2,** 339.
36. Woolacott, M. & Hoyle, G. (1977) *Proc. R. Soc. London B* **195,** 395–415.
37. Woody, C. D. & Engel, J., Jr. (1972) *J. Neurophysiol.* **35,** 230–241.
38. Woody, C. D., Swartz, B. E. & Gruen, E. (1978) *Brain Res.* **158,** 373–395.
39. Boyle, M. B., Klein, M., Smith, S. J. & Kandel, E. R. (1984) *Proc. Natl. Acad. Sci. USA* **81,** 7642–7646.
40. Sacktor, T. C., O'Brian, C. A., Weinstein, I. B. & Schwartz, J. H. (1986) *Soc. Neurosci. Abstr.* **12,** 1340.
41. Hochner, B., Schacher, S., Klein, M. & Kandel, E. R. (1985) *Soc. Neurosci. Abstr.* **11,** 29.
42. Frost, W. N., Clark, G. A. & Kandel, E. R. (1985) *Soc. Neurosci. Abstr.* **11,** 643.