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The Neuromodulatory Response: Integrating Second Messenger Pathways

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SYNOPSIS. The three themes of this chapter develop upon the nature of the neuromodulatory response. First, the neuromodulatory response is shaped by multiple second messenger pathways acting within positive and negative feedback loops. Second, second messenger pathways are interwoven, and it is their interactions that complete the feedback loops of the response. Third, the evolution of the neuromodulatory response in a special command system for a fixed action pattern of behavior is considered by comparative analysis and found to be elaborated simply from second messenger and ion conductance properties shared by many neurons.

INTRODUCTION

The long-lasting effects of neuromodulators are generally mediated by intracellular second messengers. These intermediaries act to couple membrane receptors with ion conductances through one or more enzyme steps. It is the relatively slow enzyme kinetics involved which confer the prolonged nature of the neuromodulatory response.

In the absence of extrinsic messages, second messenger pathways serve housekeeping functions in the regulation of cell activities: the rise and fall of cAMP, Ca^{2+} and H^+ during the cell cycle accompany and regulate the activities of cell division and differentiated state (Berridge, 1985; Roos and Boron, 1981; Chafouleas *et al.*, 1982). Likewise cAMP and other second messenger pathways are likely to function as elements of the circadian clocks of animals, which free run with an appropriate period in absence of day/night stimuli (Takahashi and Zatz, 1982; Prosser and Gillette, 1989). Without the governance of external modulators, second messengers act within a system of feedback loops regulating their own production and removal. When second messengers are stimulated by neuromodulators, the same feedback loops shape the neuromodulatory response.

We have studied these interactions in a pair of identified neurons of the predatory sea-slug *Pleurobranchaea californica.* These neurons appear to act in a command role in behavior: they are induced to activity by specific sensory stimulation of neuromodulatory pathways and they act to drive an easily recognized adaptive behavior. Thus, the documented interactions of the second messenger pathways are set within a context where the functional significance of the pathways to the regulation of neuronal excitability is well understood. The role of interactions within second messenger pathways in the generation of the features of neuronal, motor and behavioral output is the subject of the following essay.

DISCUSSION

Neuromodulatory control of a fixed action pattern of behavior: Arousal in a neural command system

Command systems, small neural networks or single neurons that drive complex, coordinated behaviors, are associated with fixed action patterns (Gillette, 1987). Fixed action patterns, as described by Lorenz, are extreme forms of behavior which are rigidly stereotyped, instinctive in origin, episodically all-or-none in expression, insensitive to sensory inputs once triggered, and transiently refractory after execution. Egg retrieval in the brooding goose is one such behavior studied by Lorenz (Lorenz, 1970); the eccentric single-mindedness the goose devotes to the act, heedless of actual consequence, moved him to

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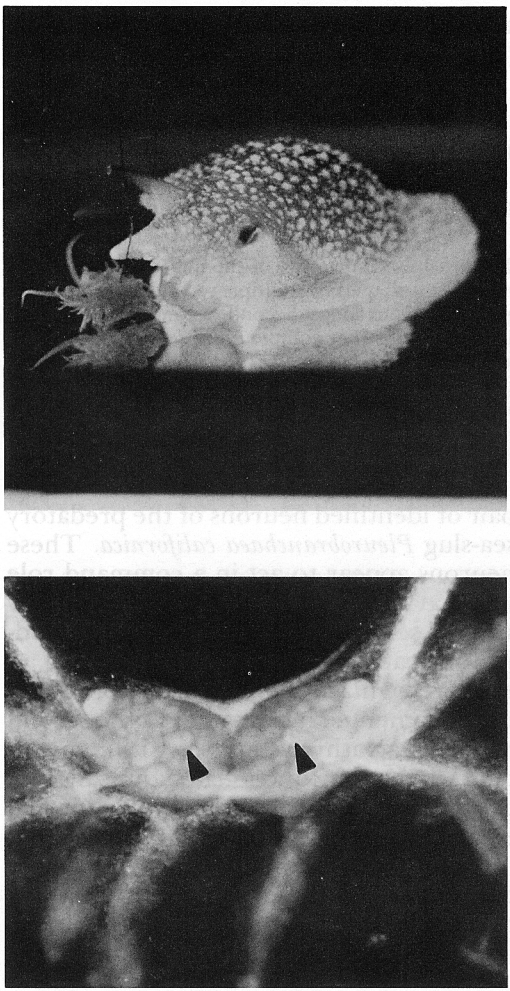

FIG. 1. *Top:* A *Pleurobranchaea* attacks the Spanish Shawl nudibranch, *Flabellinopsis iodinea. Bottom:* The ventral white cells (arrowheads) of the buccal ganglion.

give to this and similar behaviors the label of *fixed action pattern* (FAP). Humans, too, show FAP-like behaviors; a classic human FAP is the yawn. FAPs are distinguished from more versatile and generalized behaviors by their fixity and sensory isolation.

For such behaviors command systems act as feature generators for the behaviors they drive. In their activity they encode the duration and intensity of the FAP, and in some cases they may also set the timing. The major adaptive advantage of the FAP in the animal's behavioral repertory is that it is a genetically specified behavior which does not have to be learned by experience, a sometimes critical attribute. Thus, the attributes of the FAP are embedded within the animal's hard-wired neural circuitry, in some documented instances within small, highly differentiated command systems. This holds for escape locomotion in *Tritonia* (Getting, *et al.*, 1980), decapod crustaceans (Krasne and Wine, 1977) and teleost fish (Eaton and Bombardieri, 1978), for episodic respiratory pumping in *Aplysia* (Byrne, 1983), and for opportunistic gluttony in the predatory mollusk *Pleurobranchaea* (Gillette and Gillette, 1983). In each instance the command system acts to drive the motor network underlying the FAP from a hierarchic position isolated from immediate feedback of information about what the motor network is accomplishing.

The paired ventral white cells (VWCs) of the buccal ganglia of *Pleurobranchaea* drive vigorous bouts of consummatory behavior (Fig. 1). This FAP is accompanied by intensified protraction/retraction (biting and swallowing) movements of the feeding apparatus, the buccal mass. Simultaneously, through direct, crossed innervation of the esophagus/crop the VWCs cause it to mechanically prepare for receiving a large meal. The type of voracity conferred by the VWCs optimises an actively predatory foraging strategy. Such opportunistic gluttony is characteristic of many predatory carnivores. This clearly adaptive FAP is specifically triggered by food stimuli arriving in the buccal cavity.

The FAP is triggered in the following way. Chemoreception of potential food by the rhinophores, oral veil and mouth region of the animal arouses appetitive aspects of feeding: search, orientation and biting (Davis and Mpitsos, 1973; Lee and Liegeois, 1974); appetitive stimulation is largely due to the amino acids betaine (trimethylglycine) and glycine (Bicker *et al.*, 1982; Huang and Gillette, 1985), which are found in high content in its normal prey animals. The orienting, capture, and biting of appetitive behavior serve to bring food stimuli into the buccal cavity. There, food stimuli specifically act to stimulate

chemosensory pathways which have a neuromodulatory, activating effect on the VWCs (Gillette and Gillette, 1983). The actual identity of the activating neuromodulatory substance is unknown, although its action is mimicked both by histamine and octopamine (M. U. Gillette, unpublished).

Prolonged bursting and spike broadening confer command ability

Until activated, the VWCs may fire rhythmically in phase with the motor output of the feeding network, being synaptically excited by the network during the retraction phase of the movement of the feeding apparatus and inhibited during the protraction phase. Food stimuli such as an homogenate of squid introduced into the mouth cause a buildup of VWC excitability and activity until the VWC enters a minutes-long episode of rapid repetitive firing, sustained on a large plateau depolarization (Gillette and Gillette, 1983). Prolonged repetitive spike activity in the VWCs drives vigorous feeding movements in the buccal mass, seen in the force transducer record of Figure 2a accompanying a food-induced burst episode.

The ability of the VWCs to drive the motor network is absolutely dependent on a progressive, Ca^{2+}-dependent broadening of the action potential which occurs during the prolonged burst. The short, phasic bursts of spikes of the unactivated VWC have no effect on the feeding network; rather, the spikes must broaden from about 6 msec to a sharp threshold at 19–20 msec to exert any effect (Gillette *et al.*, 1980; Gillette and Gillette, 1983). The spikes may attain peak durations of several hundreds of milliseconds. The mechanisms underlying the spike broadening arise from a cumulative inactivation of the delayed rectifier K^+ current, permitting a Ca^{2+} current to prolong the spike depolarization (Gillette *et al.*, 1982*a*), as has been shown for other molluscan neurons (Aldrich *et al.*, 1979). The resulting extra Ca^{2+} entry is what underlies the VWC's ability to drive the network, presumably through enhanced transmitter release.

Once initiated, the spike activity of the VWC is insensitive to continuing synaptic inputs from the network or from mechanoreceptors which formerly drove it in cyclic activity; this is because the depolarization itself is sustained by a large increase in conductance, greater than that caused by the synaptic activity. This insensitivity to feedback from the motor network and to many sensory inputs is characteristic of known command systems and is reflected in the insensitivity of ongoing FAPs to most external influence. The VWC burst episode autoterminates within 1–5 min, and with it the bout of exceptionally vigorous behavior ends. A period ensues in which the VWC is refractory to sustaining another burst. However, in the presence of continued food stimulation the VWC's ability to support another burst episode, and drive another bout of glutting, returns. Recordings of such recurrent episodes are shown in Figure 2a.

Initially it was thought that the factors determining the ability of the VWCs to generate endogenous bursts would closely resemble those previously found to underly endogenously rhythmic activity of shorter period in other neurons (Kramer and Zucker, 1985*a*, *b*; Adams and Levitan, 1985; Lewis, 1985); however, they are rather different in several respects. The differences are related to the quite longer periods of oscillation in the VWCs, yet they arise from a specific configuration of ion channel and enzyme interrelations found in many other neurons. It is useful to consider them first for the intrinsic mechanisms which trigger and sustain the burst episode, and secondly for the mechanisms of burst termination, the post-burst refractoriness, and the recovery of the ability to burst.

Initiation and maintenance of the burst depolarization

The evidence indicates that fluctuating intracellular levels of cyclic-3′,5′-adenosine monophosphate (cAMP) determine all phases of the burst cycle, and that this intracellular messenger is an integral component of the cellular oscillator. The ability of the neurons to burst is specifically induced by cAMP (Gillette *et al.*, 1982*b*); Figure 2b, c shows a burst episode induced

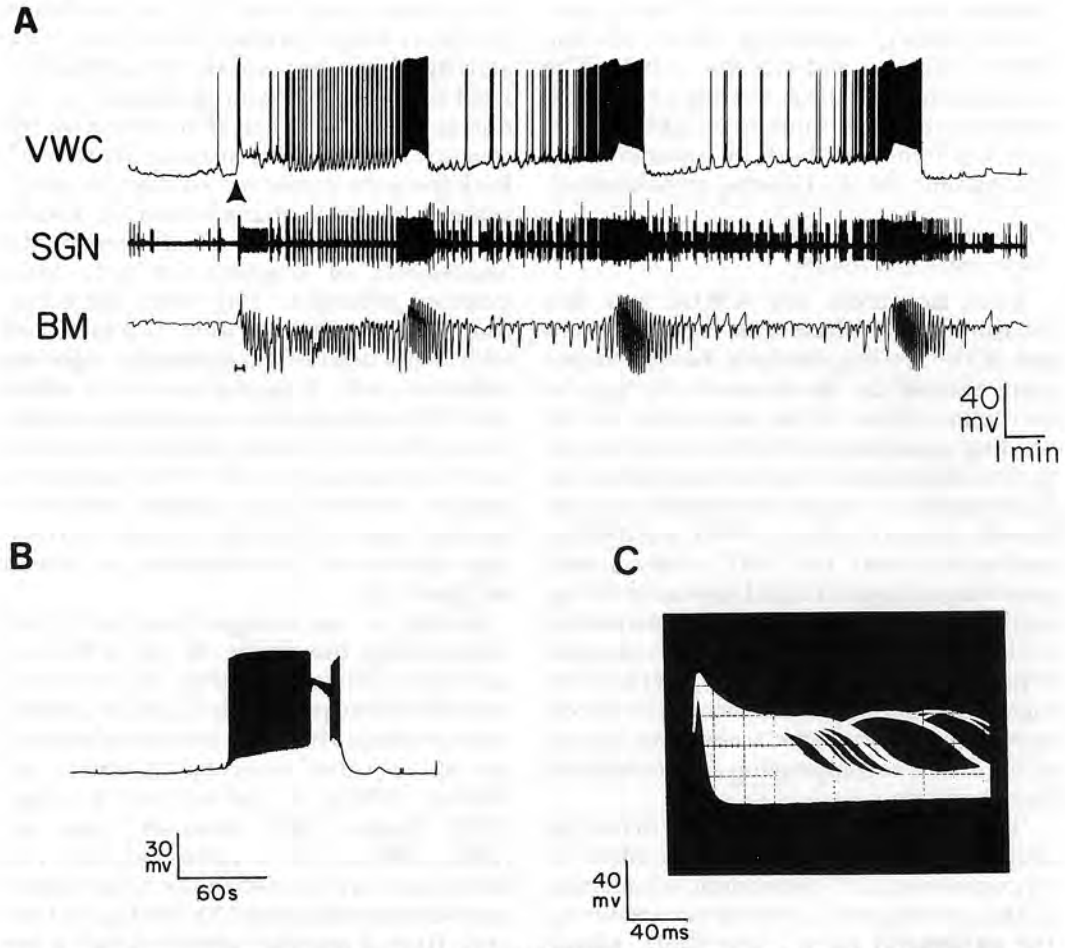

FIG. 2. A. Recurrent burst episodes recorded intracellularly from a ventral white cell (VWC) and driven feeding activity in a semi-intact animal preparation stimulated by food. Injection of squid homogenate into the buccal cavity (arrow) stimulates rhythmic movements of the buccal mass (BM), recorded by force transducer, accompanied by short, phasic bursts of VWC spikes. The occurrence of prolonged bursts of action potentials in the VWC drives episodes of more rapid and intense feeding movements. A record of the stomatogastric nerve (SGN), which carries the VWC and other axons, is also shown. B. Intracellular pressure injection of a pulse of cAMP stimulates a prolonged burst episode. C. Progressive spike broadening during a burst induced by cAMP injection. Action potentials occurring during a cAMP-stimulated burst are superimposed.

by intracellular injection of a solution of cAMP, and the accompanying spike broadening.

The burst is a direct result of the stimulation of a Na^+ current by cAMP. Intracellular injections of cAMP induce a slow, voltage-dependent inward current in the VWCs (Fig. 3a) that disappears in zero-Na^+ saline (Gillette and Green, 1987). The macroscopic current recorded in the soma is a reflection of an increase in the opening frequency of many single inward current channels; these have been recorded in the soma membrane by patch-voltage clamp methods (Fig. 3b). Some evidence from the failure of kinase inhibitors to block the current, as well as the rapid kinetics, suggests that the current is not mediated by phosphorylation, but may be like the Na^+ currents of rod photoreceptors and olfactory epithelium which are directly switched on by cyclic nucleotide binding at the channel

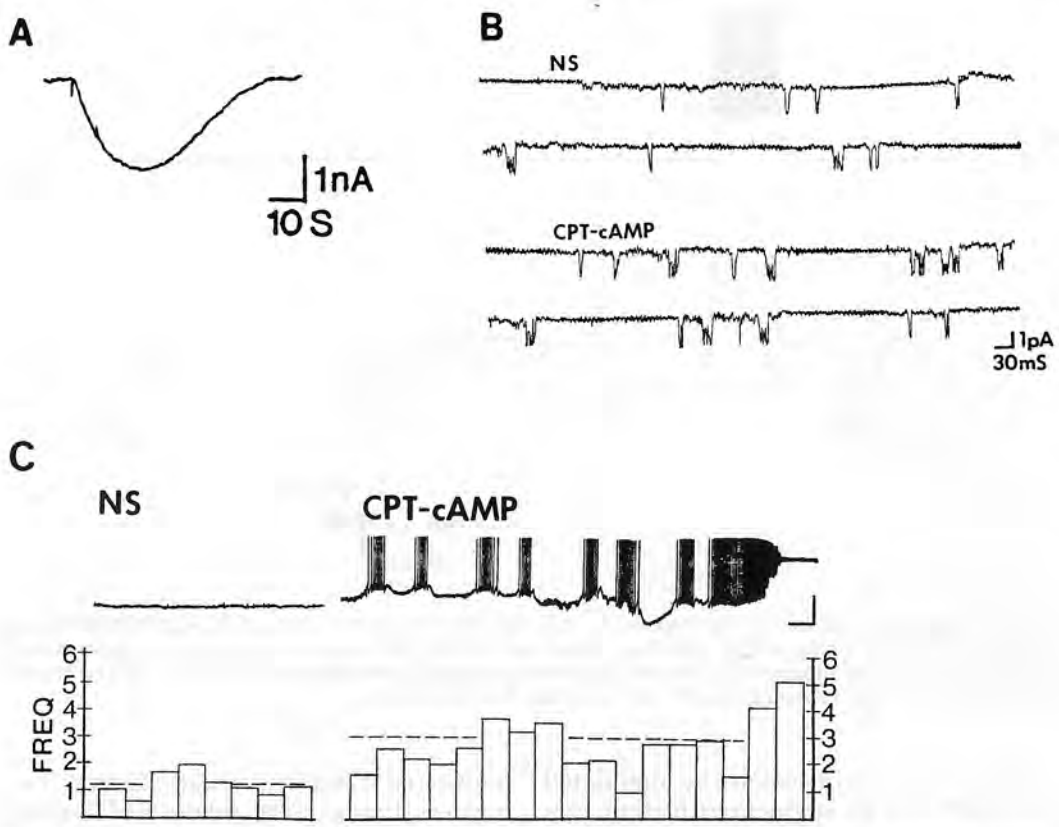

FIG. 3. A. Iontophoretic injection of cAMP (between the current artifacts) induces a net inward current which rises and decays slowly to baseline. B. Opening frequency of inward current channels in a cell-attached patch recording from the VWC in normal saline (NS) is increased by addition of a cAMP analog (CPT-cAMP) (Green and Gillette, 1983). C. Depolarization and bursting enhances cAMP stimulation of channel opening. This figure shows a frequency histogram of openings of a channel of a cell in normal saline (NS) and after bath addition of the cAMP analog 8-chlorophenylthio-cAMP. The cAMP analog increases spontaneous opening frequency, which is further augmented when the neuron enters a prolonged endogenous burst episode.

(Hockberger and Swandulla, 1987; Huang and Gillette, unpublished).

The voltage dependence of the cAMP-stimulated Na^+ current is rather complicated, multifactorial, and incompletely understood. It is not an intrinsic property of the single current channel, which is rather insensitive to membrane voltage changes (Green and Gillette, 1983). The voltage dependence is partly conferred by saline Ca^{2+}. It appears to derive in part from an extracellular binding site for Ca^{2+} whose occupation is voltage sensitive (Gillette and Green, 1987) with a dissociation constant between 10 and 20 mM at resting potential (Huang, unpublished). Possibly, this represents a voltage-sensitive block of the channel by Ca^{2+}, such that depolarization releases the block. Alternatively, depolarization could deplete the extracellular Ca^{2+} local to the external membrane through activation of the conventional voltage-dependent Ca^{2+} currents. An additional mechanism of voltage-dependence may arise from an intracellular action of Ca^{2+}. Augmentation of the opening frequency of the cAMP-stimulated Na^+ channel by depolarization occurs slowly, over a period of seconds (Fig. 3c; Green and Gillette, 1983).

The functional implication of the slow Na^+ current voltage dependence is that

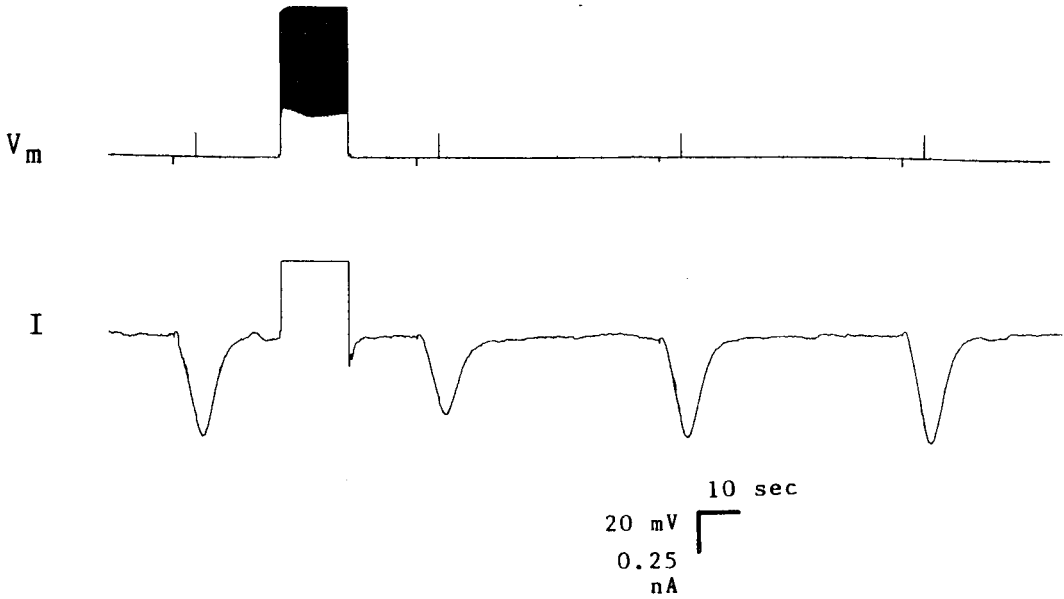

FIG. 4. Suppression of the current response by spike activity. Simultaneous records of intracellular voltage (V_m) and current (I) during cAMP injections. Following a cAMP injection, the cell is released from voltage clamp, allowed to fire progressively broadening action potentials (5–6 spikes/sec) for 15 sec, and is clamped again. The response recovers gradually over a period of a few minutes.

activity in the neuron initially stimulated by cAMP will be augmented further in a positive feedback effect. This is illustrated in Figure 3c which shows a histogram of channel opening frequency correlated with the activity of the VWC during stimulation with an analog of cAMP. As the VWC depolarizes in a burst episode the channel opening frequency increases. The cAMP analog causes an increase in the activity of channel opening as well as the spike activity; when the VWC enters a burst episode, a further increase in channel opening is correlated with the greater depolarization of the burst. Thus, the slow windup of spike frequency and increase of depolarization seen at the beginning of the burst (Figs. 2, 3) and the levels of depolarization attained during the burst are the result of the voltage dependence conferred by Ca^{2+} to the cAMP-stimulated Na^+ current.

Determinants of burst termination and refractoriness: cAMP, Ca^{+2} and pH_i

In burst generating systems in other excitable cells a Ca^{+2} activated K^+ current and in inactivating Ca^{2+} current have been implicated in burst termination and refractoriness (Lewis, 1984; Adams and Levitan, 1985; Kramer and Zucker, 1985*a*, *b*). Ca^{2+} influx during the burst augments the hyperpolarizing K^+ current and/or inactivates the depolarizing Ca^{2+} current until the cell hyperpolarizes and the burst is terminated. Subsequent removal of Ca^{2+} by buffering processes lowers the K^+ current and removes Ca^{2+} inactivation of I_{Ca}, and the cell depolarizes to the next burst threshold.

Burst termination in the VWC is also Ca^{2+} dependent, as for other bursters, but the Ca^{2+} activated K^+ current is not a major contributor, since that current is not measurable when Ca^{2+} is injected intracellularly between -100 and $+10$ mV. The main cause of burst termination and refractoriness in the VWCs appears as an activity-caused fall in the ability of cAMP to stimulate the Na^+ current. Depolarizations occurring during burst episodes or voltage clamp pulses cause suppression of the current response to injected cAMP (Fig. 4). The suppression of the cAMP response is susceptible to Ca^{2+} current blockade

(Green and Gillette, 1988). There is evidence for two Ca^{2+}-dependent mechanisms at work. One is a Ca^{2+}/calmodulin-dependent phosphodiesterase (PDE) which degrades cAMP; a second may result from another action of accumulating intracellular Ca^{2+} on the channel.

Ca^{2+} activated PDE activity proved to be present in the *Pleurobranchaea* CNS and inhibitable by calmodulin blockers (Calhoon and Gillette, 1983; Green and Gillette, 1988). In addition, the unique observation was made that the presence of Ca^{2+} caused marked pH sensitivity of PDE, with an optimum around pH 7.4–7.5 (Fig. 5). Left to discover was whether the *in vitro* pH sensitivity of PDE was matched in the living neuron.

Evidence that the living VWC itself actually has PDE activity regulated by Ca^{2+}, calmodulin and pH_i was obtained by examining inward current responses to injected cAMP under different conditions. The susceptibility of the Na^+ current response to these conditions proved to correspond to all of the salient characteristics of the PDE enzyme activity *in vitro*. The characteristic waveform of rise and decay of the inward current was enhanced and prolonged by agents which 1) alkalinize pH_i; 2) acidify pH_i; 3) reduce intracellular $[Ca^{2+}]$; 4) block the action of calmodulin; and 5) selectively block PDE (Fig. 6). The action of the PDE blocker means that in this system the rate constant of PDE activity is of major consequence in determining the excitability of the neuron. The similarity of the action of altered pH_i and calmodulin blockers indicates that the neurons contain a pH-sensitive and Ca^{2+}/calmodulin-dependent PDE.

Depolarization and discharge of neurons cause increases in the intracellular levels of free Ca^{2+} and H^+, due to activation of Ca^{2+} current and H^+ generating processes that buffer intracellular Ca^{2+} (Ahmed and Connor, 1980; Meech and Thomas, 1980). In view of this, it might be expected that the suppression of the cAMP response by depolarization would arise from PDE activation. However, while it is fairly certain that a variety of treatments are able to suppress PDE activity, as yet there is no convincing evidence that the activity is really enhanced by Ca^{2+} influx. This is because the temporal duration of the cAMP response is unaffected by depolarizing pulses (Green and Gillette, 1988)—enhanced PDE activity should shorten it. Presently it seems likely that PDE activation is an important factor in the normal function of the neuron, but Ca^{2+} leaks resulting from multiple electrode penetrations in the voltage clamp experiments may cause saturation of enzyme activity.

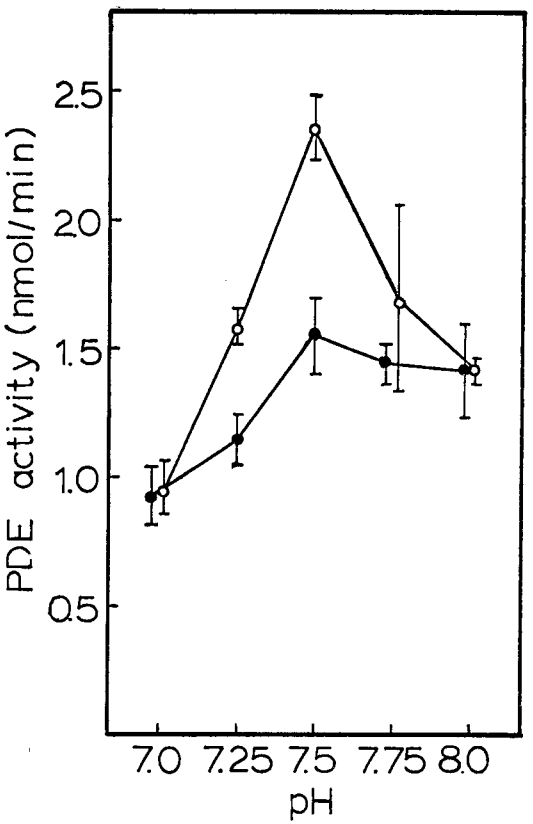

FIG. 5. Ca^{2+} activated and pH sensitive phosphodiesterase activity in CNS extracts of *Pleurobranchaea*. Addition of excess Ca^{2+} (open circles) to aliquots containing the chelator EGTA both increases cAMP hydrolysis and enhances pH sensitivity (Calhoon and Gillette, 1983).

Thus, suppressive effects of intracellular Ca^{2+} may be mediated directly at the level of the channel. This is a novel mechanism for termination of bursting activity, adding another task for Ca^{2+} to its long list of

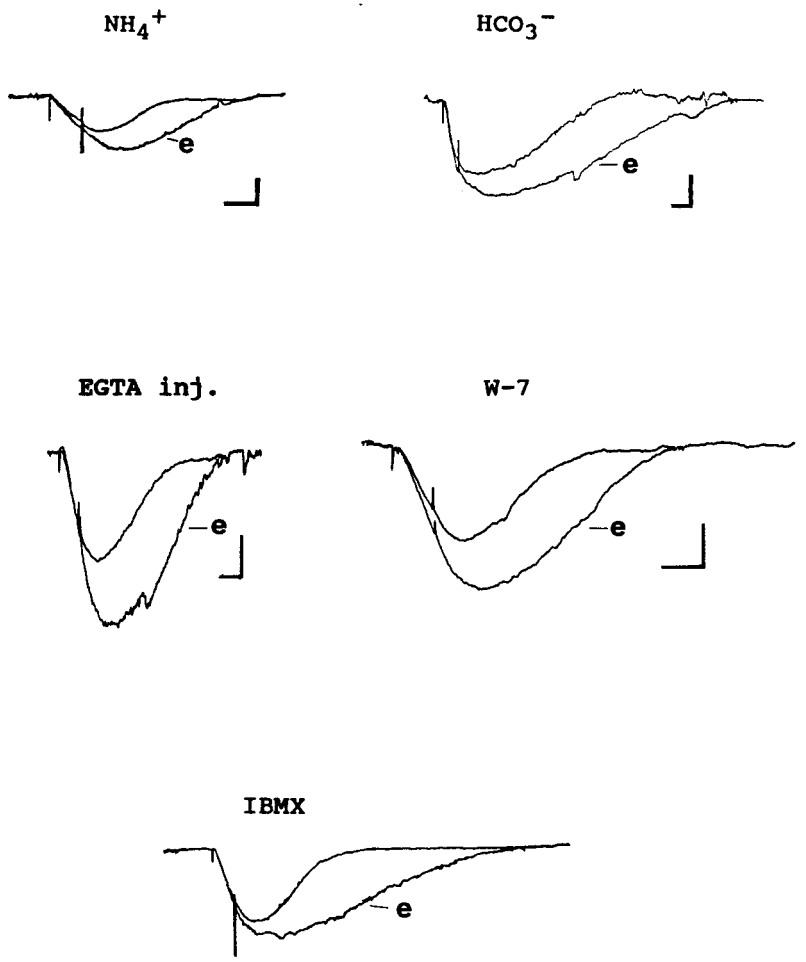

FIG. 6. Phosphodiesterase inhibition is mimicked by altering intracellular pH, lowering intracellular [Ca^{2+}], and calmodulin blockade. The records are superimposed recordings of cAMP responses elicited before and after experimental (e) treatments. *Top left:* Intracellular alkalinization by bath addition of 15 mM ammonium chloride. *Top right:* Intracellular acidification by bath addition of 15 mM sodium bicarbonate. Changes in the current are detectable at pH changes less than 0.05 unit. *Middle left:* Intracellular injection of the Ca^{2+} chelator, EGTA (67 mM, buffered to pH 7.3 in 1 M MOPS). *Middle right:* Bath addition of the calmodulin blocker W-7 (50 μM). *Bottom:* Bath addition of the phosphodiesterase blocker isobutylmethylxanthine. *Calibrations:* Horizontal, 5 sec; vertical, 0.5 nA.

responsibilities in cell function. But there remains still another Ca^{2+}-dependent effect, which acts to antagonize the suppressive effect of Ca^{2+} on the channel current in the presence of high levels of cAMP. When cAMP levels are kept tonically high, an interaction between cAMP and Ca^{2+} occurs so as to reverse the negative effects of Ca^{2+} influx on the cAMP response (Huang and Gillette, 1987). The response may be even enhanced over control levels. Such an effect is shown in Figure 7.

An integrative model of the actions of cAMP, Ca^{+2}, pH_i, and phosphodiesterase in neuronal activity and behavior

Our present picture of the interactions of the processes which regulate the command role in the VWCs is summarized graphically in the model of Figure 8. It can be laid out simply in several steps:

1) An early step in burst initiation is an increase in levels of intracellular cAMP, due to activation of the synthetic adenylate

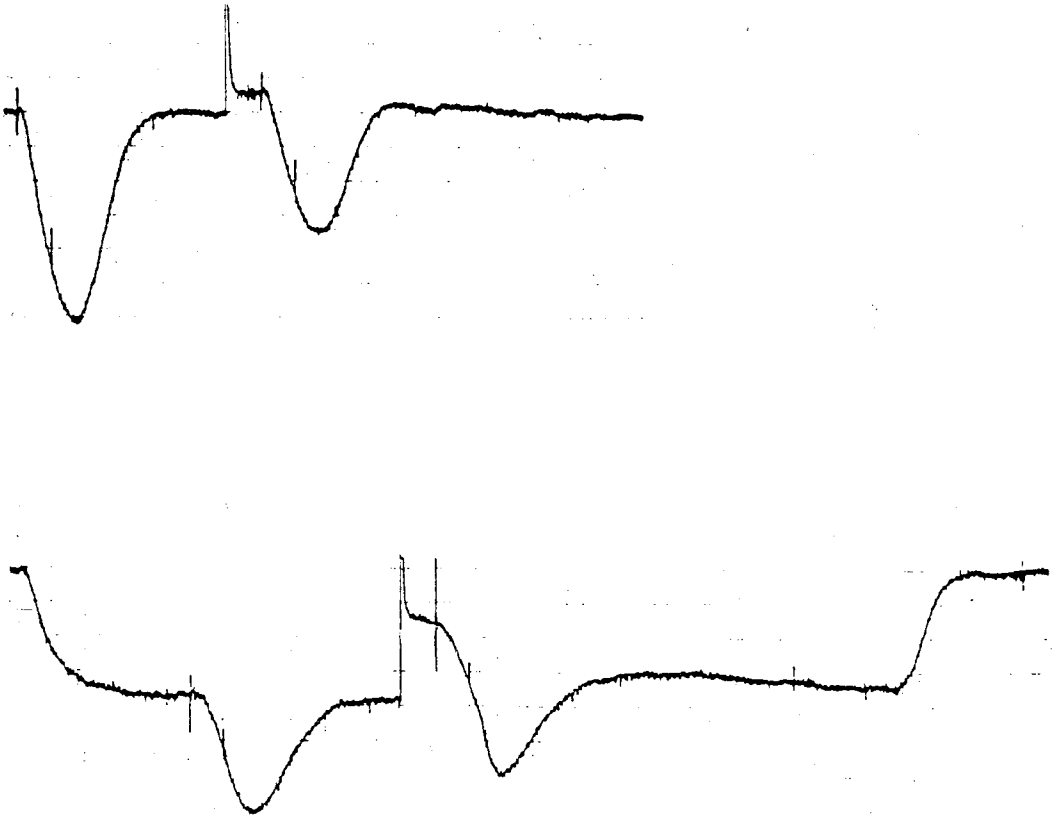

FIG. 7. *Upper record:* Depolarization suppression of the cAMP response. cAMP responses before and after a 100 msec voltage pulse to +10 mV, in a neuron of the pedal ganglion. Following the pulse, the response amplitude is decreased for several minutes. *Lower record:* A repeat of the above experiment in the presence of tonically high levels of cAMP causes a reversal of the depolarization suppression phenomenon. Test injections of cAMP and depolarizing pulses are superimposed on a background current caused by prolonged iontophoretic injection of cAMP.

cyclase enzyme (AC) by activity in neuromodulatory pathways.

2) The increase in the slow Na^+ current, caused by cAMP stimulation, drives electrical activity of the cell, which in turn leads to Ca^{2+} influx and an increase in free intracellular Ca^{2+}.

3) Initially, the dominant effect of depolarization is to potentiate the inward current, in one way by lifting a depolarization-sensitive Ca^{2+} block of the channel, and also through intracellular effects of accumulating Ca^{2+} exerted at the level of the ion channel. (Calmodulin blockers do not suppress the potentiating effect of Ca^{2+} on the inward current, which excludes a possible role for most Ca^{2+}-dependent kinases known.) The positive feedback effect of depolarization leads to greater depolarization and spike activity, and further Ca^{2+} influx.

4) Increased levels of intracellular Ca^{2+} depress channel activation by cAMP. They also lead to an intracellular acidification through activation of proton-generating Ca^{2+} buffering processes, Ca^{2+}/H^+ competition for binding sites, and perhaps other processes. This leads to PDE activation.

5) Augmented PDE activity causes a fall in cAMP levels, a consequent fall in the slow inward current which sustains the burst, and hyperpolarization of the membrane potential by the K^+ and Cl^- conductances of the cell.

6) The post-burst refractory period reflects the interval during which Ca^{2+} and

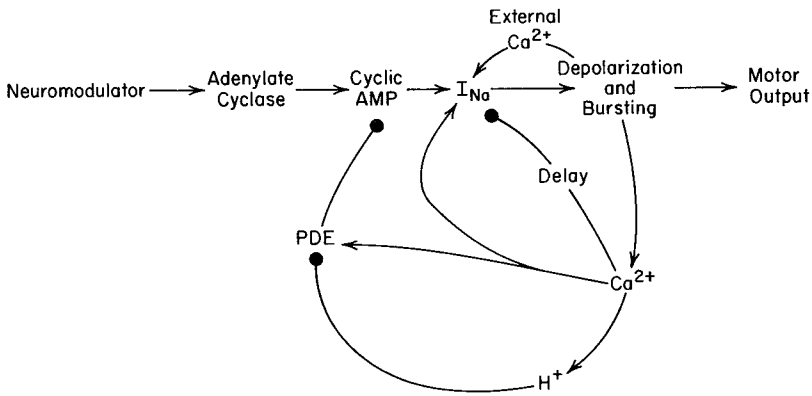

FIG. 8. A model incorporating mechanisms contributing to the neuromodulatory response and command function of the VWCs. Arrows indicate stimulatory actions, filled circles indicate suppressive or inhibitory actions. Detail is to be found in the text.

H^+ buffering processes permit the decline of PDE activity and the recovery of cAMP to levels which can support another burst.

Thus, the burst is initiated by cAMP; the duration and the termination of the burst episode in the VWC may be seen as determined in large part by a progressive buildup in Ca^{2+} activity. This results in a decline in cAMP and a consequent decline in cAMP-dependent inward current. It is notable that Ca^{2+} has two opposing roles in this system: In burst initiation through potentiating cAMP-dependent slow inward current, and in burst termination through decreasing it. The interactions of cAMP, PDE, Ca^{2+} and H^+ form a negative feedback loop with the basic characteristics of a single-phase oscillator, consistent with the ability of the activated VWC to burst in recurrent episodes.

Phylogeny and evolution of the neuromodulatory response in Pleurobranchaea

Salient features of the fixed action pattern of opportunistic gluttony in *Pleurobranchaea* are thus attributable to simple interactions of metabolism, conductance channels and ions. The relationships described here depict the determination of a complex behavioral pattern through interactions of only a few basic mechanisms. Our wide-ranging comparative studies in progress have so far suggested that the behavioral role of the VWC is unique to *Pleurobranchaea,* even among its putative homologs in other opisthobranch snails. What can be said about the evolution of such a specialized command system?

First, the command system and its neuromodulatory features probably coevolved with the behavior. The extreme features of the physiology of the VWC are paralleled in the extremity of the vigorous feeding behavior of *Pleurobranchaea,* relative to the milder table manners of its opisthobranch cousins. *Pleurobranchaea,* an opportunistic predator with the taste and habits of a sea-going hyena, tends to catch and gobble its food quickly in ravenous bouts of opportunistic gluttony. Most other seaslugs are specialists who feed exclusively on sessile organisms which hold still long enough to be savored in a manner allowing efficient grazing. Since other neurons in the networks of opisthobranchs have clear homologs identifiable among the various species (Gillette and Davis, 1977; Dickinson, 1979, 1980; see Watson and Groome, 1989), identification and comparative study of homologs of the VWC in other animals might cast light on the evolution of its neuromodulatory response.

Very likely homologs of the VWC are found in notaspidean opisthobranch species closely related to *Pleurobranchaea.* The nervous systems and feeding apparatus of *Berthella plumula, Pleurobranchus membranaceus,* and *Berthellina citrina* all show a great deal of similarity, and each lobe of the buccal ganglia has a prominent white cell with

ventral soma and contralateral axon innervating the esophagus. However, of these four species only *Pleurobranchaea* shows vigorous episodes of actively predatory gluttony; the others tend to ruminate thoughtfully on non-motile tunicates. Similarly, only the ventral white cells of *Pleurobranchaea* show marked spike broadening during repetitive firing and have the capacity to drive vigorous output of the feeding motor network. Thus, this would support the contention that in *Pleurobranchaea* the habit of rapacious feeding has specialized in evolution along with its neural command system (Gillette, 1987).

That which is special about the VWC of *Pleurobranchaea*, as suggested by preliminary analyses, is a greater manifestation of a Ca^{2+} current and very little evidence of a Ca^{2+}-activated K^+ current. The cAMP-stimulated Na^+ current that underlies the VWC burst episodes is widely distributed among neurons of the feeding motor network, as is the pH-sensitive phosphodiesterase. Other membrane currents are not unusually different from neurons which do not show the marked spike broadening and very prolonged burst episodes of the VWC. Thus, although the comparative data are preliminary as yet, they indicate that the VWCs of *Pleurobranchaea* are evolutionary specializations of motor network elements whose ancestral physiology was not especially remarkable. Possibly, elaboration of the distinctive physiology of the VWCs in evolution was largely accomplished by simply enhancing the number of Ca^{2+} channels and diminishing the number of Ca^{2+}-activated K^+ channels. Such a simple regulation of the expression of as few as two genes may have far-reaching consequences for the messenger roles of Ca^{2+} and its interactions with other second messengers; this remains for future exploration.

CONCLUSION

When considering neuromodulatory actions at both behavioral and cellular levels, two characters which sculpt the form of the neuromodulatory response should be kept in mind. First, the second messenger pathways that mediate neuromodulatory actions generally are not one-way transmitters of effect from receptor to cell output. Rather, second messengers are elements of feedback loops within the cell whose levels may influence their own synthesis and degradation, or influx and efflux. Second, because second messenger pathways of action and inactivation may involve multiple enzyme steps, there are multiple sites at which activity of any given second messenger may be regulated by the action of other second messenger systems. Thus while a "second messenger" is commonly thought of as an intracellular mediator of a primary, extrinsic signal, stimulation of one pathway can alter the others with both feedback and feedforward effects.

Insofar as the physiology of neurons may be affected in evolution, preliminary evidence supports the idea that marked specialization is effected through simple regulation of the amplitude of a second messenger signal and of the kind and amount of its targets within the neuron.

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