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ORIGINAL CONTRIBUTION

Small Networks of Empirically Derived Adaptive Elements Simulate Some Higher-Order Features of Classical Conditioning

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Abstract—*Previously, we developed a single-cell mathematical model of the sensory neurons in* Aplysia *(Gingrich & Byrne, 1985, 1987). This single-cell model accurately simulated many aspects of empirically observed neuronal plasticity that contribute to simple forms of nonassociative and associative learning. In the present study, we incorporated this empirically derived adaptive element into small networks and examined the ability of these networks to simulate second-order conditioning and blocking. When the single-cell model was incorporated into a three-cell network (Hawkins & Kandel, 1984), we found that constraints imposed by the empirical data limited the ability of the network to simulate both second-order conditioning and blocking. On the other hand, we found that the detailed descriptions of subcellular processes unmasked phenomena relevant to the simulation of blocking, that are not captured by less detailed models. We also incorporated the model of the sensory neuron into a lateral inhibition-type network consisting of five elements. This network successfully simulated both second-order conditioning and blocking more readily than the three-cell network.*

Keywords—*Aplysia*, Blocking, Lateral inhibition, Learning, Models, Neural networks, Second-order conditioning, Sensory neurons.

1. INTRODUCTION

Computer simulations of neural networks have proven to be a valuable tool in helping to understand how assemblies of neurons may perform the wide spectrum of adaptive information processing observed in biological systems (e.g., Bienenstock, Cooper & Munro, 1982; Desmond & Moore, 1988; Fukushima, Miyake & Ito, 1983; Gelperin, Hopfield & Tank, 1985; Gelperin, Tank & Tesauro, 1989; Grossberg, 1988; Grossberg & Levine, 1987; Hopfield, 1982; Klopf, 1988; Pearson, Finkel & Edelman, 1987; Sejnowski & Rosenberg, 1986; Sutton & Barto, 1981). Many models of neural networks are composed of simple interconnected elements that take the weighted sum of their inputs and generate an output via an activation function. The weights between network elements change according to a "learning rule." While this approach has been successful, a fundamental issue in neural network modelling, which has not been addressed adequately, is the level of detail necessary to model individual neurons and how such detail affects the global properties of networks.

One way of addressing this issue is to examine the ability of neural networks consisting of elements based on the detailed properties of neurons to simulate a well-defined task for which empirical data are available. One such well-defined task is classical conditioning. The parametric features of classical conditioning have been examined extensively, and thus, there is a large body of data with which the performance of the network can be compared. Moreover, cellular mechanisms underlying some forms of associative plasticity have been identified, and thus, it is becoming possible to incorporate detailed descriptions of the cellular processes involved in neuronal plasticity into the individual elements of the neural networks.

During first-order classical conditioning (e.g., Mackintosh, 1974; Pavlov, 1927), an animal is pre-

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sented with repeated temporal pairings of a neutral conditioned stimulus (CS; e.g., a bell) and an unconditioned stimulus (US; e.g., food). The US reflexively elicits an unconditioned response (UR; e.g., salivation). During training, the animal establishes a relation between the CS and the US, and the CS comes to elicit a conditioned response (CR), which is similar in nature to the UR. A neural analogue of first-order classical conditioning has been identified at the sensory to motor neuron synapses in *Aplysia* and is termed activity-dependent neuromodulation (Hawkins, Abrams, Carew & Kandel, 1983; Walters & Byrne, 1983). During activity-dependent neuromodulation, activation of a sensory neuron (analogous to the CS) in contiguity with a unconditioned or reinforcing stimulus (the US) results in an enhancement of the excitatory postsynaptic potential (EPSP; analogous to the CR) in the follower motor neuron. The cellular mechanisms for activity-dependent neuromodulation appear to emerge from the synergistic action of two intracellular second messenger systems, cAMP and Ca^{2+} (for reviews see Abrams & Kandel, 1988; Byrne, 1985, 1987). The reinforcing stimulus acts via a facilitatory neuron to increase the intracellular levels of cAMP in the sensory neurons, and in turn, cAMP leads to an enhancement of the synaptic strength of the sensory neurons. The entry of Ca^{2+} during the CS (spike activity in the sensory neurons) primes the US-mediated increase in cAMP levels.

Although considerable progress has been made in elucidating the neural basis of classical conditioning, little is known about the neural mechanisms responsible for higher-order features of classical conditioning such as second-order conditioning (Pavlov, 1927; Rescorla, 1980), blocking (Kamin, 1968, 1969) and contingency (Rescorla, 1968). Several quantitative models of small neural networks have shown that, in theory, the same learning rules capable of simulating classical conditioning can simulate higher-order features of classical conditioning (e.g., Byrne, Buonomano, Corcos, Patel & Baxter, 1988; Gluck & Thompson, 1987; Grossberg & Levine, 1987; Hawkins, 1989a,b; Klopf, 1988; Sutton & Barto, 1981, 1990). A conceptual model proposed by Hawkins and Kandel (1984) is based on plastic properties and circuitry found in *Aplysia*. They propose that the relatively simple rules that seem to guide simple associative and nonassociative plasticity in *Aplysia* can serve as building blocks for higher-order features of classical conditioning. According to this hypothesis, higher-order features of classical conditioning emerge from the interactions of a few adaptive elements in small networks.

In this paper, we examine the ability of networks consisting of elements based on the activity-dependent neuromodulation learning rule to simulate two higher-order features of classical conditioning, second-order conditioning and blocking. To do this, we use a previously described model of the *Aplysia* sensory neurons that quantitatively simulates empirical data on various forms of nonassociative and associative synaptic plasticity (Byrne & Gingrich, 1989; Byrne, Gingrich & Baxter, 1989; Gingrich & Byrne, 1985, 1987; Gingrich, Baxter & Byrne, 1988). Our approach is to incorporate this adaptive element into plausible networks, and make a minimum of assumptions regarding the properties of the nonadaptive elements within the circuit. When the single-cell model was incorporated into a three-cell network (Hawkins & Kandel, 1984), we found that the constraints imposed by the empirical data limited the ability of the network to simulate second-order conditioning and blocking. On the other hand, we found that a detailed description of subcellular processes unmasked phenomena that are relevant to the simulation of blocking, that are not captured by less detailed models. We also incorporated the model of the sensory neuron into a lateral inhibition-type network consisting of five elements. This network successfully simulated both second-order conditioning and blocking more readily than the three-cell network. A preliminary report of these results has been presented (Byrne et al., 1988).

2. THREE-CELL NETWORK

2.1 Description of the Elements

The general properties of the adaptive element are illustrated in Figure 1. The equations used in this single-cell model are provided in the Appendix and have been described in detail previously (Byrne & Gingrich, 1989; Byrne et al., 1989; Gingrich & Byrne, 1985, 1987). The model consists of differential equations describing two pools of transmitter, a releasable pool (P_R) and a storage pool (P_S). Vesicles of transmitter are mobilized from P_S to P_R via three fluxes, one driven by diffusion (F_D), another driven by Ca^{2+} (F_C) and the third driven by cAMP (F_{cAMP}). There are also differential equations describing the regulation of the levels of cAMP and Ca^{2+}. Action potentials lead to influx of Ca^{2+} (I_{Ca}), which in turn mediates the release of transmitter (T_R). Ca^{2+} influx also leads to an increase in the intracellular concentration of Ca^{2+}, which modulates both mobilization of transmitter and synthesis of cAMP. The facilitatory transmitter induces the synthesis of cAMP, which in turn modulates both mobilization of transmitter and the duration of action potentials. Pairing spike activity in a sensory neuron (the representation of the CS) with stimulation of the facilitatory neuron (the representation of the US) leads to increased levels of cAMP. In turn, cAMP leads to the enhancement of transmitter release in response to sub-

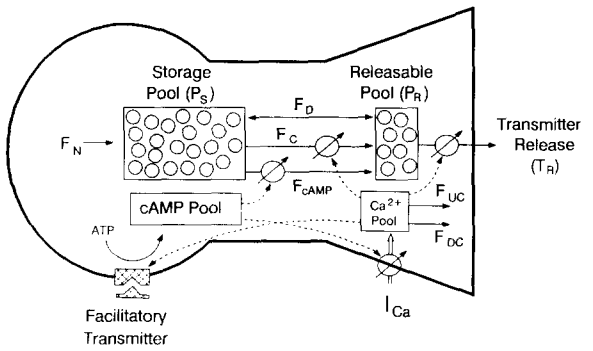

FIGURE 1. Components of the single-cell model that is described by Gingrich and Byrne (1985, 1987). Action potentials lead to the opening of Ca^{2+} channels and to a subsequent increase in the Ca^{2+}-current (I_{Ca}). The Ca^{2+} influx leads to an increase the level of intracellular Ca^{2+} (Ca^{2+} pool), which triggers transmitter release, mobilization of transmitter (F_C) from a storage (P_S) to a releasable (P_R) pool, and primes the synthesis of cAMP produced by the facilitatory transmitter. F_D represents diffusion of vesicles between the storage and the releasable pools. The US results in the release of a facilitatory transmitter that induces the synthesis of cAMP, which in turn enhances mobilization of transmitter (F_{cAMP}) and increases the influx of Ca^{2+} during spike activity. Increased Ca^{2+} influx (I_{Ca}) is achieved indirectly through cAMP-dependent changes in spike duration. Paired presentation of the CS and US results in increased levels of cAMP due to priming of cAMP synthesis by Ca^{2+}. The pairing-specific elevated levels of cAMP produces increased mobilization of transmitter and spike broadening beyond that produced by the facilitatory transmitter alone. Consequently, when subsequent action potentials are elicited there is enhanced Ca^{2+} influx and release of transmitter. The circles with arrows through their center represent elements of the model that are modulated by other variables. Unless otherwise noted all equations and parameters are as described in Gingrich and Byrne (1985, 1987; see also Appendix).

sequent activation of the sensory neuron. This model quantitatively simulates empirical data on synaptic depression, heterosynaptic facilitation, and associative plasticity of the sensory to motor neuron synapse in *Aplysia* (Gingrich & Byrne, 1985, 1987). Unless otherwise noted, all equations and parameters used in the present simulations are described by Gingrich and Byrne (1985, 1987; see also Appendix).

The single-cell model was initially incorporated into a three-cell network consisting of two identical sensory neurons and one facilitatory neuron (Figure 2). Activity in each modeled sensory neuron represents a separate CS pathway (i.e., CS1 and CS2). The sensory neurons make excitatory connections with the facilitatory neuron. An important consequence of this connection is that a sensory neuron can take control of the facilitatory neuron as the strength of the sensory to facilitatory neuron connection increases. This property has important implications with respect to models of higher-order features of classical conditioning (Grossberg, 1971; Hawkins & Kandel, 1984). The function of the facilitatory neuron is to provide a modulatory output in response to input from both the US and sensory neurons. The facilitatory neuron is the neural representation of the reinforcing stimulus (Grossberg, 1971; Hawkins & Kandel, 1984). Because there are few experimental data on the properties of the facilitatory neuron, it was not modeled at the same level of detail as the sensory neurons. As a first approximation, we modeled the facilitatory neuron as a simple element that integrates postsynaptic responses produced by each of the sensory neurons. The response of the postsynaptic membrane (V_{EPSP}) to released transmitter was approximated as an RC circuit with a time constant (T_M) of 100 ms;

$$\frac{dV_{EPSP}}{dt} = \frac{T_{R1} + T_{R2} - V_{EPSP}}{T_M}, \qquad (1)$$

where T_R represents the release of transmitter from the respective sensory neurons. If V_{EPSP} is greater than an assigned threshold, the facilitatory neuron releases a facilitatory transmitter that induces cAMP synthesis in each sensory neuron (see Figure 1). As suggested by Hawkins and Kandel (1984), an assumed property of the facilitatory neuron is that its output decays or accommodates as a function of time. Accommodation was modeled by a parameter termed

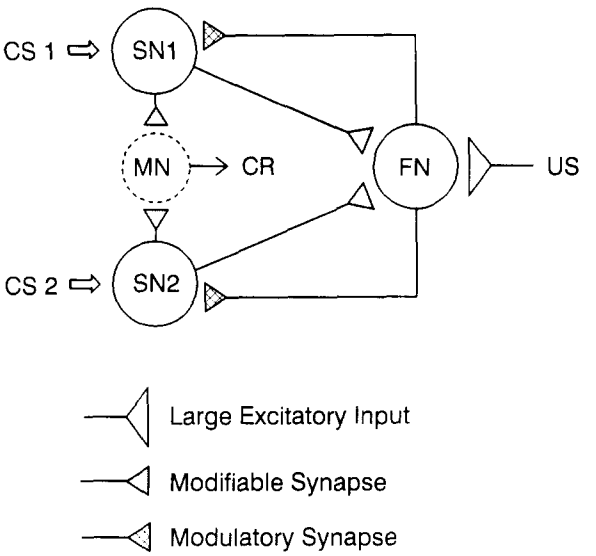

FIGURE 2. The model of the sensory neuron that is shown in Figure 1 was incorporated into a circuit consisting of two identical sensory neurons (SN1 and SN2) and a facilitatory neuron (FN). The sensory neurons can be activated independently by separate conditioned stimuli (CSs). The facilitatory neuron is activated by the US and can also be activated by a sensory neuron if the level of the input exceeds threshold. The facilitatory neuron is a nonplastic element that releases a transmitter which in turn induces the synthesis of cAMP in the sensory neurons. Sensory neuron input to the motor neuron (MN) and facilitatory neuron represent the conditioned response (CR). Since the input to the facilitatory neuron and MN are identical we only simulated the facilitatory neuron in order to simplify the network. Although not illustrated the US also produces strong excitation of the MN.

Q, that varies from 1 to 0. During the time that either V_{EPSP} is suprathreshold or the US is on, Q decays according to:

$$\frac{dQ}{dt} = \frac{-Q}{T_{Q1}} \tag{2}$$

and when V_{EPSP} falls below threshold, the facilitatory neuron recovers from accommodation, and Q increases according to:

$$\frac{dQ}{dt} = \frac{1 - Q}{T_{Q2}}, \tag{3}$$

where T_{Q1} is the time constant for accommodation and T_{Q2} is the time constant for recovery from accommodation. Throughout this paper, the values of T_{Q1} and T_{Q2} are set at 50 ms and 10 s, respectively. Thus, when the facilitatory neuron is activated by the US its output decays to zero within approximately 200 ms (see Figure 4b). Within approximately 40 s, the facilitatory neuron fully recovers from accommodation. The output of the facilitatory neuron results in the synthesis of cAMP in the sensory neurons.[1]

2.2 Simulations of the Three-Cell Network

The defining feature of second-order conditioning is that a conditioned stimulus (CS1) can come to function as a reinforcing stimulus for the conditioning of a second conditioned stimulus (CS2; Pavlov, 1927; Rescorla, 1980). In second-order conditioning, animals are trained in two phases. During Phase I, a conditioned stimulus (CS1) is paired with a US (i.e., first-order conditioning of CS1). During Phase II, a novel conditioned stimulus (CS2) is paired with CS1 and there is no presentation of the US (i.e., second-order conditioning of CS2). After training, CS2, which was never paired with a US, can come to elicit a CR.

The training paradigms used in our simulations of second-order conditioning are illustrated in Figure 3. During Phase I of second-order conditioning (Figure 3a), the CS1 cell (CS1 +) is activated 280 ms (the optimal ISI) before the onset of the US, while the CS2 cell (CS2 −) is activated 15 s before the onset of the US. Each CS consisted of a 400-ms train of 11 spikes at a frequency of 25 Hz in the modeled sensory neurons. The duration of the US is 200 ms (Gingrich & Byrne, 1987; Walters & Byrne, 1983). During Phase II of second-order conditioning (Figure 3a), the CS2 cell is activated 280 ms before the onset of CS1, and no US is presented. Phase I and II consisted of 5 and 10 trials, respectively, and the intertrial interval is fixed at 5 min. The control paradigm for second-order conditioning is similar to the experimental paradigm except that during Phase I, the CS1 is presented in an unpaired fashion with the US (Figure 3b).

In our simulations, the threshold of the facilitatory neuron proved to be a critical parameter (see below). With low thresholds, the network simulated second-order conditioning, but not blocking. Conversely, with a high threshold, the network simulated a small degree of partial blocking, but not second-order conditioning. A simulation of second-order conditioning with a low threshold facilitatory neuron is illustrated in Figure 4. During Phase I (Trials 1–5), the EPSPs produced in the facilitatory neuron by both the CS1 and CS2 cells (SN1 and SN2, respectively) show increases in strength (Figure 4a). The increase in strength of the EPSP produced by the CS2 cell is due to a nonassociative effect (the neural equivalent of sensitization). The CS1 cell, which was paired with the US, displays a larger increase than that observed in the CS2 cell (first-order conditioning of CS1). During Phase II (Figure 4a, Trials 6–15), the presentation of the US is terminated and activity in the CS2 cell is paired with activity in the CS1 cell. During Phase II, the strength of the CS2 cell is enhanced. Towards the end of Phase II, the strengths of both the CS1 and CS2 cells begin to extinguish. As illustrated by the control paradigm (dotted line), if the CS1 cell is unpaired with the US during Phase I, then there is no enhancement of strength in the CS2 cell during Phase II.

Changes in the synaptic outputs of the two sensory neurons and the facilitatory neuron during the simulation of second-order conditioning are illustrated in Figure 4b. Initially, the EPSPs produced by the CS1 cell or the CS2 cell are small and subthreshold for activation of the facilitatory neuron, which is activated only by the US (Figure 4b, Trial 1). By the end of Phase I (Figure 4b, Trial 5), however, the EPSP produced by the CS1 cell is large enough to activate the facilitatory neuron. CS1 can now function as a reinforcing stimulus for the conditioning of CS2 by activating the facilitatory neuron (Figure 4b, Trial 6). Consequently, the magnitude of EPSP2 increases as activity in the CS2 cell is paired with activity in the CS1 cell (Figure 4b, Trial 10). Thus, second-order conditioning in this network results from the ability of a previously conditioned CS to

[1] In the previous model of Gingrich and Byrne (1987), the US was simulated with a rectangular pulse having a duration of 200 ms. In the present simulations, the US is an identical rectangular pulse but due to eqn (2) the effective US (the output of the facilitatory neuron) is a decaying exponential. In order for the effective US to produce the same level of first-order conditioning as in Gingrich and Byrne (1987), we adjusted the parameters in the equation that describes the amount of cAMP synthesis produced by the US (eqn (A16)). Specifically, K_{SC} was increased by a factor of 4.0 and K_{EC} of the same equation by a factor of 3.7.

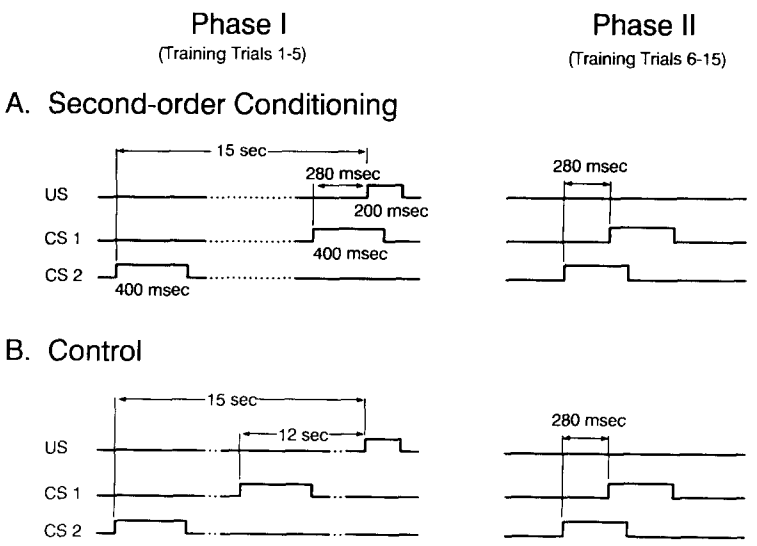

FIGURE 3. Training paradigms used in the simulations of second-order conditioning and the control for second-order conditioning. (a) During Phase I of second-order conditioning, CS1 (spike activity in SN1) is temporally paired with the US (ISI of 280 ms), while CS2 is presented in a unpaired fashion (ISI of 15 s). During Phase II, CS2 is paired with CS1 in the absence of any US. (b) The control paradigm for second-order conditioning is similar to the experimental paradigm except that CS1 is unpaired with the US during Phase I (ISI of 12 s). Since the adaptive elements used in our simulations exhibit significant nonassociative plasticity, equivalent to sensitization and habituation, our results are easier to interpret when CS2 is presented during Phase I, but unpaired with the US. The results remain unchanged when we use controls in which CS2 is not activated during Phase I.

take control of the facilitatory neuron and serve as a reinforcer for the conditioning of a second CS (Grossberg, 1971; Hawkins & Kandel, 1984).

Blocking is a higher-order feature of classical conditioning that emphasizes the predictive value of the CS in relation to the US (Kamin, 1968, 1969). A blocking paradigm consists of two phases of training. During Phase I, a conditioned stimulus (CS1) is temporally paired with the US. During Phase II, CS1 and a second conditioned stimulus (CS2) are presented simultaneously (a compound stimulus; CS1/CS2) and paired with the US. With training, CS1 continues to elicit a conditioned response, while CS2, produces little or no conditioned response, even though it was temporally paired with a US. Thus, preconditioning of CS1 "blocks" the conditioning of the CS2 component of a CS1/CS2 compound from conditioning.

The training paradigms used in our simulations of blocking are illustrated in Figure 5. During Phase I, the CS1 is paired with the US (CS1+), while CS2 is presented in an unpaired fashion (CS2−; Figure 5a). During Phase II, both CS cells are activated simultaneously, 280 ms before onset of the US. The control paradigm (Figure 5b) is similar to the experimental paradigm except that during Phase I, both CS1 and CS2 are presented in an unpaired fashion with the US.

With a high threshold of the facilitatory neuron, the three-cell network was able to simulate partial blocking (Figure 6). During Phase I (Figure 6a, Trials 1–5), the CS1 cell (SN1) exhibits first-order conditioning and the CS2 cell (SN2) exhibits sensitization. During Phase II (Figure 6a, Trials 6–15), the CS2 cell initially exhibits less conditioning than the control (dotted line), which represents a small degree of partial blocking. Figure 6b illustrates the outputs of the sensory neurons and facilitatory neuron after various periods of training. Initially, the EPSPs produced by SN1 and SN2 are weak, and thus, neither CS cell is strong enough to activate the facilitatory neuron, which is only activated by the US (Figure 6b, Trial 1). The decrease in the release of facilitatory transmitter (FN Output) during the presentation of the US represents accommodation (eqn (2)). The facilitatory neuron recovers completely from accommodation within an intertrial interval. After first-order conditioning, the EPSP produced by CS1, while enhanced, is still subthreshold for activation of the facilitatory neuron (Figure 6b, Trial 5). During Trial 6, both CS1 and CS2 cells are activated simultaneously and their summed EPSPs are able to activate the facilitatory neuron. Due to the incomplete recovery from accommodation, the output of the facilitatory neuron in response to the US is decreased. Thus, the CS2 cell undergoes less conditioning than it would have if CS1 had not been preconditioned (control trace in Figure 6a). In addition, because the compound CS activates the facilitatory neuron, the effective ISI has shifted from 280 ms to zero. A 0-s ISI is less effective because the Ca^{2+} levels in a cell are relatively low during the time of activity in the facilitatory neuron.

As mentioned above, the threshold of the facili-

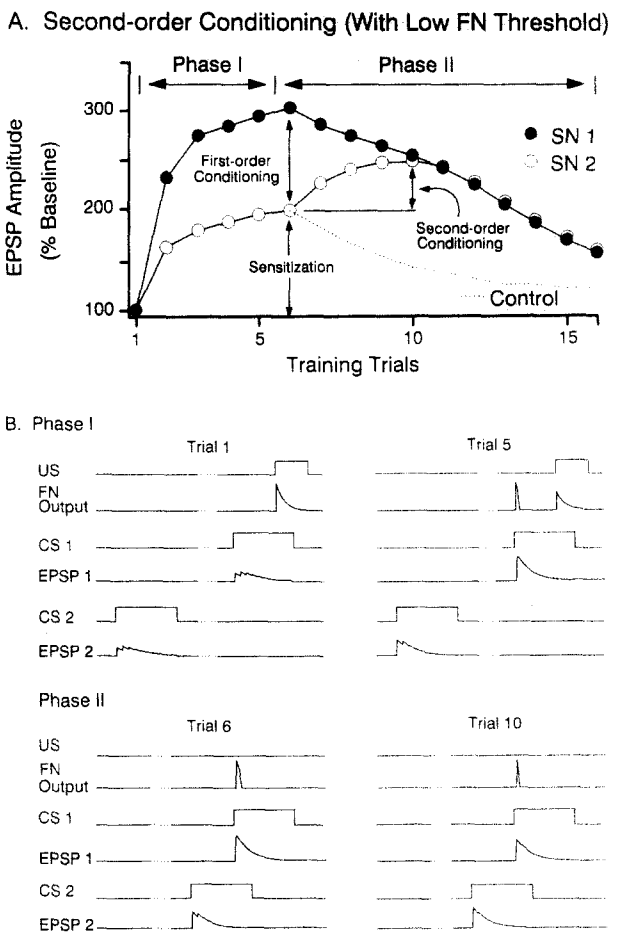

FIGURE 4. Simulations of second-order conditioning with a low threshold of the facilitatory neuron. (a) The baseline values of the EPSPs produced by the CS cells were normalized to 100%. During first-order conditioning (Phase I, Trials 1–5), both the CS1 cell (SN1) and CS2 cell (SN2) show increases in strength. The increase in strength observed in the CS2 cell is due to a nonassociative effect (sensitization). The CS1 cell, which was paired with the US, is enhanced to a greater extent. During Phase II (Trials 6–15), the EPSPs produced by CS2 exhibited an increase in strength due to second-order conditioning. During Phase I, of the control paradigm, both CS cells exhibit a nonassociative increase in strength. Phase II of the control paradigm (dotted line) illustrates that without preconditioning of CS1 no associative plasticity is observed in the CS2 cell. (b) The outputs of the sensory neurons and facilitatory neuron are plotted at various points during training. Initially, neither CS cell is strong enough to activate the facilitatory neuron, which is activated only by the US (Trial 1). By the end of first-order conditioning, CS1 is able to activate the facilitatory neuron (Trial 5). The CS1 cell can now function as a reinforcing stimulus by activating the facilitatory neuron and condition the CS2 cell (Trial 6). Towards the end of Phase II, the associative plasticity in both cells begins to extinguish (Trial 10). Note that the duration of the CS outlasts the actual duration of the EPSPs. This is due to synaptic depression. The threshold of the facilitatory neuron was 1100.

tatory neuron is a critical parameter for simulating second-order conditioning and blocking. The examples given (Figures 4 and 6) used different thresholds, each of which was selected for either maximal second-order conditioning or blocking. The ability of the three-cell network to simulate both second-order conditioning and blocking as a function of the threshold of the facilitatory neuron is illustrated in Figure 7. No single threshold permitted reasonable simulations of both second-order conditioning and blocking. Lower thresholds permitted second-order conditioning because the CS1 + cell could easily activate the facilitatory neuron, and thus provide reinforcement for conditioning of the CS2 cell (Figure 4). Blocking, on the other hand, could not be simulated with a low threshold, since both the CS1 + /CS2 − compound (experimental) and the CS1 − /CS2 − compound (control) could activate the facilitatory neuron. Thus, the CS2 − cell during both the control and experimental blocking paradigms exhibited the same degree of conditioning. Higher thresholds, within a range, improve the degree of blocking. This improvement occurs because the CS1 + /CS2 − compound activates the facilitatory neuron, partially shifting its activity to a time that is less effective for inducing associative plasticity in the CS2 − cell, while the CS1 − /CS2 − compound of the control will induce little or no shift. Second-order conditioning, however is not simulated when the facilitatory neuron has a high threshold because CS1 + is not able to activate the facilitatory neuron (e.g., Figure 6b, Trial 5).

Thus, by implementing our single-cell model of an *Aplysia* sensory neuron into a neural network suggested by Hawkins and Kandel (1984), it was possible to simulate either second-order conditioning or a small degree of blocking; depending on the threshold of the facilitatory neuron. Both phenomena, however, could not be simulated adequately with the same threshold of the facilitatory neuron.

An analysis of the above results revealed that there are at least three constraints that must be satisfied in order to simulate both second-order conditioning and complete blocking with this type of network.

1. *No conditioning should occur with an ISI of zero seconds.* With the Hawkins–Kandel hypothesis, the degree of blocking is intrinsically related to the ISI function and the accommodation of the facilitatory neuron. In order to obtain complete blocking there can be no overlap between activity of the facilitatory neuron and a functional associative trace within the CS2 − cell. Thus, either the facilitatory neuron must accommodate very rapidly, or the minimal functional ISI must be relatively large. Complete blocking can occur if the CS1 + /CS2 − compound fully activates the facilitatory neuron in order to produce complete accommodation, and during the time it takes the facilitatory neuron to accommodate, the CS2 − cell is not in a state receptive to associative plasticity. This relation was also stressed by Gluck and Thompson (1987).

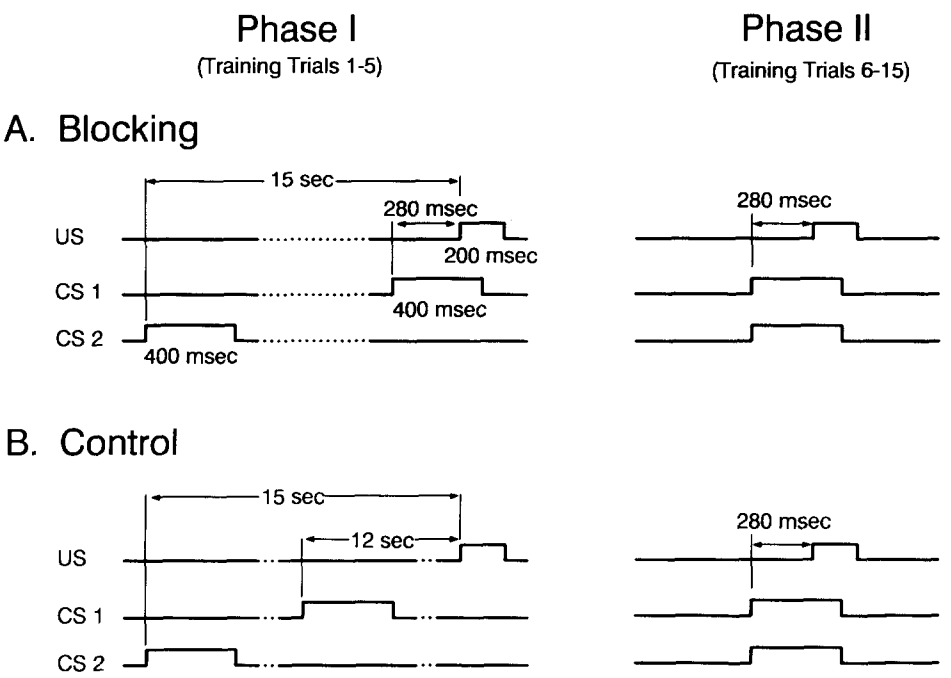

FIGURE 5. Training paradigms used in the simulations of blocking and the control for blocking. (a) Blocking paradigm. During Phase I of blocking, CS1 is paired with the US (ISI of 280 ms) and CS2 is presented in an unpaired fashion with the US (ISI of 15 s). During Phase II, both CS1 and CS2 are presented simultaneously and paired with the US. (b) The control paradigm for blocking is similar to the experimental paradigm except that during Phase I CS1 is unpaired with the US (ISI of 12 s).

2. *The strength of a* CS+ *cell should be at least twice as large as that of a* CS− *cell.* To obtain complete blocking, the CS1+/CS2− compound must shift the time window of activation of the facilitatory neuron, but the CS1−/CS2− compound of the control should not. If the first compound stimulus of a control simulation (CS1−/CS2−) activates the facilitatory neuron, a type of "pseudo-blocking" is obtained in which the CS2 cell would not condition with either a CS1+/CS2− compound of a blocking simulation or with the CS1−/CS2− compound of a control simulation. In addition, the CS1+ must be able to activate the facilitatory neuron in order to obtain second-order conditioning. Thus, in order for the three-cell network to account for both second-order conditioning and blocking several conditions relevant to the strengths of the CSs and the threshold of the facilitatory neuron must be satisfied: (i) the CS1+/CS2− should strongly activate the facilitatory neuron; (ii) the CS1−/CS2− compound should not activate the facilitatory neuron; (iii) the CS1+ stimuli should at least partially activate the facilitatory neuron. These three conditions imply that the strength of a CS1+ cell must be at least twice as great as the strength of a CS2− cell, and that the threshold of the facilitatory neuron must lie between the strength of CS1+ and CS1+/CS2−.

3. *The* CS1+ *cell should be able to strongly activate the facilitatory neuron.* A further factor particular to our empirically derived model, was the depletion of transmitter from the sensory neuron. In the train of eleven spikes that constituted the CS, the first one or two spikes of the CS1+ cell would release enough transmitter to reach the threshold of the facilitatory neuron, but, due to depletion of transmitter, the effects of the later spikes were relatively weak (see EPSPs and output of the facilitatory neuron in Figure 4b, Trial 5). Thus, it proved difficult for a sensory neuron to maximally activate the facilitatory neuron for a period of time of greater than about 100 ms.

3. THREE-CELL NETWORK WITH A MODIFIED SINGLE-CELL MODEL OF A SENSORY NEURON

3.1 Modifications of Element Properties

We next modified our original models of the sensory and facilitatory neurons in order to satisfy the above constraints. Although the modifications described below are physiologically plausible, it should be emphasized that they are not based on experimental data.

1. *Threshold of* Ca^{2+} *concentration for associative plasticity.* Our original model exhibited an optimal ISI of 280 ms and some conditioning at an ISI of 0 s (see Figure 8). We modified the properties of the sensory neuron by assuming that Ca^{2+} must reach a critical concentration before it can prime cAMP synthesis and thus induce associative plasticity. We assumed that Ca^{2+} must reach a level that is achieved

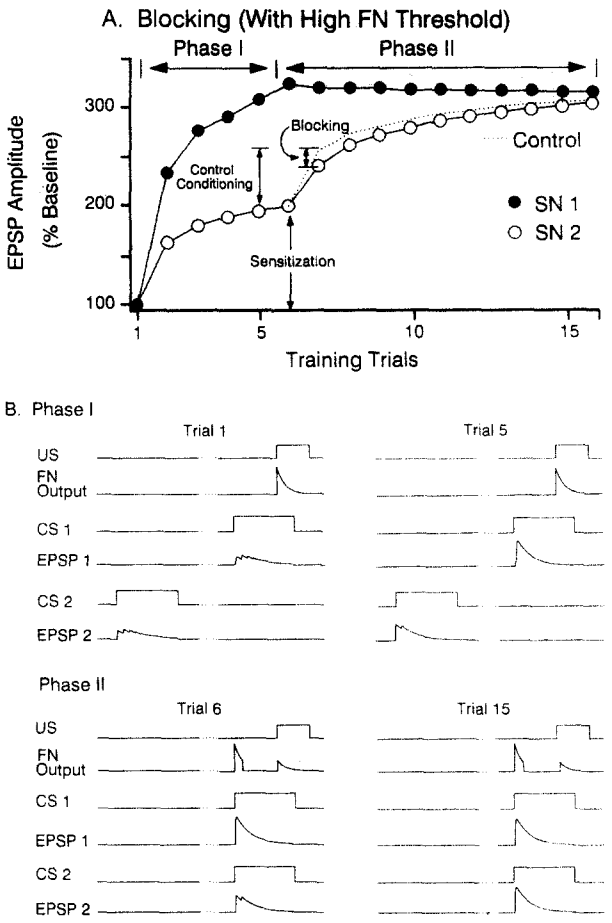

FIGURE 6. Simulation of blocking with a high threshold of the facilitatory neuron. (a) During Phase I (Trials 1–5), the CS1 cell exhibits first-order conditioning while the CS2 cell exhibits nonassociative plasticity (sensitization). During Phase II (Trials 6–15), the CS2 cell exhibits slightly less conditioning than the control (dotted line), representing a small degree of partial blocking. (b) The output of the sensory neurons and facilitatory neuron are shown during different training trials. Initially, neither CS cell is strong enough to activate the facilitatory neuron, which is activated only by the US (Trial 1). After first-order conditioning the EPSP produced by CS1 is still subthreshold for activation of the facilitatory neuron (Trial 5). During Trial 6, both the CS1 and CS2 cells are activated simultaneously and their summed output is able to activate the facilitatory neuron and induce its partial accommodation. Thus, the facilitatory neuron can only be partially activated when the US is presented. Since, the facilitatory neuron output in response to the actual US is decreased, less associative plasticity occurs in the CS2 cell. The threshold of the facilitatory neuron was 1500.

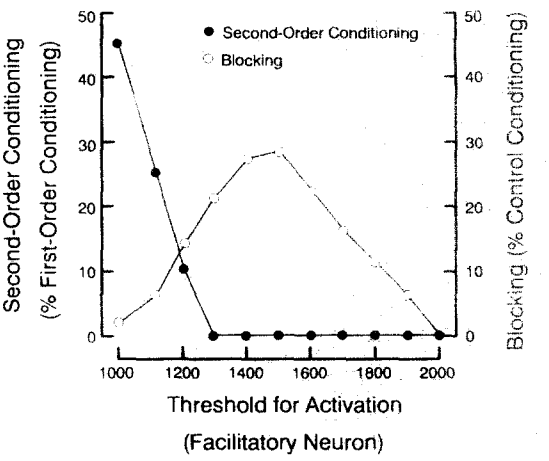

FIGURE 7. Degree of second-order conditioning and blocking as a function of threshold of the facilitatory neuron. Second-order conditioning is measured as the percentage of maximum first-order conditioning (e.g., Figure 4a). Blocking is measured as the difference of control and experimental conditioning in relation to the control at Trial 7 (see Figure 6a). Thus, 0% blocking indicates there was no difference between the conditioning of the CS2 cell in the control and experimental simulations, whereas 100% blocking would indicate that the CS2 cell did not exhibit any conditioning (i.e., complete blocking).

by a naive cell as a result of approximately 300 ms of stimulation.[2] As can be seen in Figure 8 this modification shifted the rising phase of the ISI function 250 ms to the right, eliminating conditioning with an ISI of 0 s.

2. *Increase in magnitude of associative plasticity*. The constant for Ca^{2+}-dependent cAMP synthesis was increased and the constant for Ca^{2+}-independent cAMP synthesis was decreased.[3] These parameter modifications increased the difference in strength between a CS1+ and a CS2− cell by increasing the degree of associative plasticity and decreasing nonassociative plasticity.

3. *Enhanced* cAMP*-dependent mobilization of transmitter*. In our initial simulations, when a CS1+ cell was stimulated, all spikes following the third or fourth released little transmitter due to depletion. In order to decrease depletion of transmitter, we enhanced cAMP-dependent mobilization of transmitter from the storage to releasable pool.[4] In addition, the duration of the CS was also increased from 11 spikes (400 ms) to 21 spikes (800 ms) to further enhance associative plasticity.

4. *Burst-like property in facilitatory neuron*. As mentioned above, one of the reasons we failed to obtain reasonable blocking was that the CS1+/CS2− compound was not able to maintain activity in the facilitatory neuron. To overcome this limitation, we incorporated a burst-like property in the facilitatory neuron. Specifically, the duration of activity in the

[2] The C_{Ca} variable (eqn (A7)) must attain the value of 0.6555 before associative plasticity occurred.

[3] This was done by decreasing the K_{SC} constant from 1600 to 600 and increasing the K_{EC} from 5360 to 9900 (see Appendix).

[4] This was done by adding the term: $8 \cdot 10^{-4} \cdot C_{cAMP}$ to the F_S equation of the original model (see Appendix) and by increasing the gain constant of the F_{cAMP} equation (K_{FC}, eqn (A12)) from $2 \cdot 10^{-6}$ to $8 \cdot 10^{-6}$.

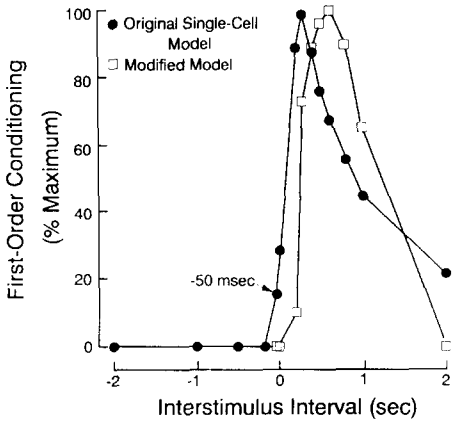

FIGURE 8. Effects of the interstimulus intervals on first-order conditioning of original and modified single-cell models. First-order conditioning was plotted as percentage of maximal conditioning (i.e., conditioning at the optimal ISI). Introduction of a Ca^{2+} threshold for associative plasticity in the modified single-cell model shifted the ISI function to the right preventing associative plasticity at an ISI of 0 s.

facilitatory neuron was made a linear function of the time period that the input of the facilitatory neuron remained above threshold.[5] With this modification, the facilitatory neuron fires for a time proportional to the period V_{EPSP} is above threshold.

The above assumptions were made with the objective of obtaining complete blocking and second-order conditioning with the three-cell network. We chose to focus on complete blocking in order to obtain a systematic analysis of blocking. A model that simulates complete blocking can simulate partial blocking, while the converse is not true. Experimental data of conditioned suppression in rats shows both partial and complete blocking (e.g., Kamin, 1968; Mackintosh, 1975).

3.2 Simulations of Three-Cell Network with Modified Elements

When the three-cell network was simulated with the above modifications, the following changes were observed in relation to first-order conditioning: (1) there was no conditioning with a CS–US interval of 0 s, and the optimal ISI was shifted from 280 ms to approximately 500 ms (Figure 8); (2) the model did not continue to quantitatively simulate the empirical data on associative plasticity (Gingrich & Byrne, 1987; Walters & Byrne, 1983) because the ratio of associative to nonassociative plasticity was increased (e.g., Figure 9a); (3) the influence of the ISI on the shape of the acquisition curve during first-order conditioning was more pronounced. Nonoptimal ISIs tended to display sigmoid acquisition functions, whereas optimal ISIs displayed negatively accelerating acquisition functions. The simulations described in this section were carried out with an ISI of 480 ms, a value that resulted in a negatively accelerating acquisition curve.

The three-cell network that incorporated the modified single-cell model was able to simulate both second-order conditioning and complete blocking with a single threshold of the facilitatory neuron. Figure 9 illustrates the simulation of second-order conditioning. During Phase I (Figure 9a, Trials 1–5), the CS1 cell (SN1) exhibits first-order conditioning and the CS2 cell exhibits a small degree of sensitization. During Phase II (Figure 9a, Trials 5–16), the strength of the CS2 cell increases as a result of second-order

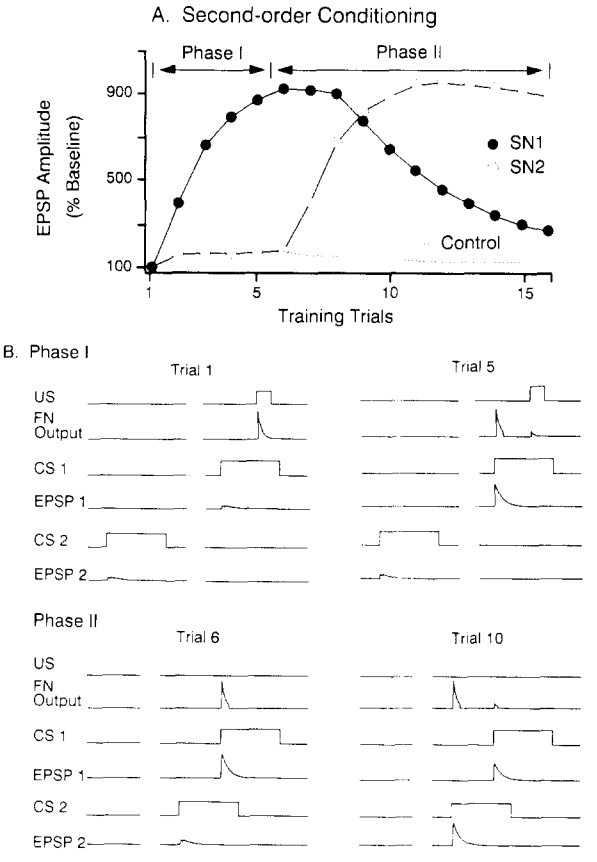

FIGURE 9. Simulation of second-order conditioning with the modified three-cell network. (a) During first-order conditioning (Phase I, Trials 1–5), the CS1 cell exhibits an increase in strength which is much greater than that in the original single-cell model (compare with Figure 4a). During Phase II (Trials 6–15), the CS2 cell exhibits second-order conditioning. (b) The outputs of the sensory neurons and facilitatory neuron are plotted at various points during training. Initially, the EPSPs from neither CS cell are large enough to activate the facilitatory neuron, which is activated only by the US (Trial 1). By the end of first-order conditioning, CS1 is able to strongly activate the facilitatory neuron (Trial 5), and thus function as a reinforcing stimulus for conditioning of the CS2 cell (Trial 6). The threshold of the facilitatory neuron was 2000.

[5] The duration of activity in the facilitatory neuron was equal to the time that the input remained above threshold multiplied by 1.5.

conditioning. The EPSPs produced by the sensory neurons and the output of the facilitatory neuron are illustrated in Figure 9b. By the end of Phase I, the EPSP produced by the CS1 cell is strong enough to activate the facilitatory neuron, and thus the CS1+ cell is able to serve as a reinforcing stimulus for the conditioning of CS2 during Phase II (Figure 9b, Trial 6). Note that during Phase II of second-order conditioning, the associative strength of the CS2 cell becomes sufficiently large to activate the facilitatory neuron (Figure 9b, Trial 10). Consequently, the CS2 cell receives some "self-reinforcement" and its extinction is slowed (Figure 9a). Since CS2 activates the facilitatory neuron and causes its accommodation, the CS1 cell receives less reinforcement (Figure 9b, Trial 10) and its associative strength extinguishes more rapidly (Figure 9a).

Figure 10 illustrates a simulation of blocking with the same threshold of the facilitatory neuron that was used in the simulation of second-order conditioning (Figure 9). During Phase I (Figure 10a, Trials 1–5), the CS1 cell (SN1) exhibits first-order conditioning and the CS2 cell exhibits a small degree of sensitization. During Phase II (Figure 10a, Trials 6–15), CS2 exhibits no conditioning. Thus, the CS2 cell exhibited complete blocking. In contrast, during the control paradigm (dotted line) each cell conditioned to approximately 50% of the strength observed during first-order conditioning. Figure 10b illustrates the output of the sensory neurons and the facilitatory neuron during various periods of training. Initially, the EPSPs produced by either CS cell are not strong enough to activate the facilitatory neuron, which is activated only by the US (Figure 10b, Trial 1). After first-order conditioning, the EPSP produced by the CS1 cell is strong enough to activate the facilitatory neuron, but not strong enough to fully accommodate it (Figure 6b, Trial 5). During Phase II (Figure 10b, Trial 6), the summed input from SN1 and SN2 activates the facilitatory neuron. Due to the accommodation of the facilitatory neuron produced by the compound CS, the output of the facilitatory neuron in response to the actual US is insignificant. Thus, the CS2 cell essentially receives a 0-s pairing with the reinforcement, which does not produce any associative plasticity in the CS2 cell. If, however, the onset of CS2 precedes CS1 during Phase II, blocking does not occur. In this paradigm, the CS2 is not receiving a reinforcement at a 0-s ISI, and can undergo associative plasticity (simulations not shown). This phenomenon has been described by Kehoe, Schrueurs and Graham (1987).

An unexpected result was that this model was able to simulate complete blocking with a negatively accelerating acquisition function. As shown by Gluck and Thompson (1987), a difficult aspect of simulating complete blocking is that the CS2− cell should not

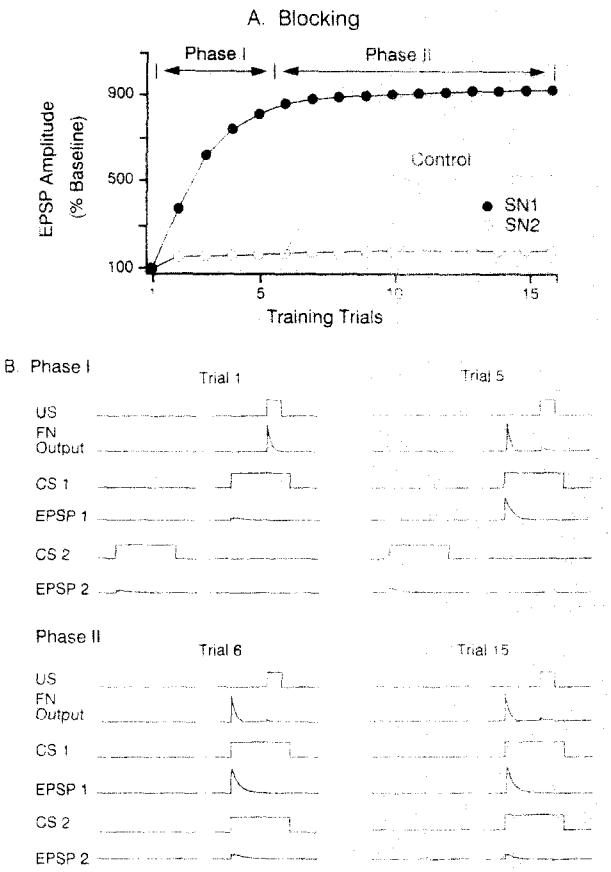

FIGURE 10. Simulation of blocking with the modified three-cell network. (a) During Phase I, CS1 exhibits first-order conditioning. During Phase II, CS2 exhibits complete blocking (i.e., the CS2 cell does not exhibit any increase in strength). The output of each sensory neuron of the control paradigm (dotted line) exhibits conditioning and reaches an asymptote at approximately 50% of that observed during first-order conditioning. Thus, the summed strength of both cells is approximately equal to that observed in first-order conditioning. (b) In contrast to the previous model (Figure 6), it can be seen that during Trial 6 the CS1+/CS− compound produces full accommodation of the facilitatory neuron. Consequently, the US does not significantly activate the facilitatory neuron. The CS2 cell does not undergo any conditioning because it is activated simultaneously with the facilitatory neuron (an effective ISI of zero). The CS1 cell however, undergoes associative plasticity because it enters a state receptive to associative plasticity sooner due to quicker influx of Ca^{2+}. The threshold of the facilitatory neuron was 2000.

undergo any associative plasticity during Phase II, but the CS1+ cell must undergo associative plasticity in order to counterbalance extinction (see also Discussion). This property is achieved in our simulations because the CS+ cell has broader action potentials, and thus a more rapid influx of Ca^{2+}. This permits the CS1+ cell to reach its critical concentration of Ca^{2+}, within a time period that the facilitatory neuron is still active. In contrast, the CS2 cell, which has not been conditioned, has narrow spikes, and thus, it takes a longer period of time during the CS

to reach the critical levels of Ca^{2+} necessary for associative plasticity. Indeed, the CS2− cell requires approximately 300 ms to reach its critical Ca^{2+} concentration, and by that time the facilitatory neuron is inactive (e.g., Figure 10b, Trial 6). Consequently, at the time the facilitatory neuron is activated by the CS1+/CS2− compound during the Phase II of blocking, no conditioning of a CS2− occurs.

An interesting finding that emerged from the simulation of complete blocking with the modified three-cell network is that during Phase II the actual US had no functional influence, since the compound CS resulted in complete accommodation of the facilitatory neuron (e.g., Figure 10b, Trial 6). A corollary of this is that the CS1+ of a CS1+/CS2− compound does not extinguish in the absence of a US; a feature that is biologically implausible. With minor changes of parameter values (such as decreasing the magnitude of Ca^{2+}-dependent cAMP synthesis) this model can simulate arbitrarily good partial blocking in which extinction is observed. Partial blocking occurs when the CS1+/CS2− compound does not fully accommodate the facilitatory neuron.

It is interesting to note that in the original single-cell model described by Gingrich and Byrne (1987) the asymptote of the acquisition curve resulted from the saturation of intracellular Ca^{2+} concentrations, which caused cAMP to reach a steady state. As noted by Hawkins (1989a,b), with the introduction of connections between the sensory neurons and facilitatory neuron, and accommodation of the latter, an asymptote is reached due to a shift in the time period of activation of the facilitatory neuron. That is, as the strength of the CS1+ increases with conditioning, the facilitatory neuron is activated within a time period closer to the onset of the CS. On one hand, the shift in facilitatory neuron activity causes a deacceleration of the acquisition curve, since as the onsets of the CS and the US become closer there is less associative plasticity. On the other hand, as training progresses, the levels of cAMP are increased, and action potentials are broadened, thus increasing the rate at which Ca^{2+} accumulates. This process tends to create a positive feedback, such that with each trial there is an increase in the influx of Ca^{2+} and an increase in synthesis of cAMP. Whichever of these antagonistic processes is more pronounced determines whether the acquisition function is a sigmoidal or a negatively accelerating curve. In our simulations with the modified three-cell network, nonoptimal ISIs (either long or short) produced little conditioning on the first trial of first-order conditioning, thus the shift in facilitatory neuron activity would be relatively small or nonexistent, resulting in a sigmoid function. Conditioning with an optimal ISI, however, exhibited a negatively accelerating acquisition function because the first trial of first-order conditioning was enough to cause a significant temporal shift in the activation of the facilitatory neuron. A further prediction of these simulations is that the ISI functions can be state dependent; cells that have previously received reinforcement will have different time courses of Ca^{2+} influx, and thus different optimal ISIs.

4. LATERAL INHIBITION MODEL

4.1 Circuit Description

In an attempt to develop a network that simulated both second-order conditioning and blocking, and retained the ability to simulate the available empirical data (Gingrich & Byrne, 1985, 1987), we constructed a network in which inhibitory neurons were added in a lateral inhibition-type architecture (Figure 11). In this circuit, each model sensory neuron excites an inhibitory neuron (IN) which in turn inhibits the neighboring sensory neuron.

As a first step, we assumed that the inhibitory neurons inhibited the associative plasticity in the sensory neurons. This is a hypothetical mechanism that could occur at numerous loci, such as blocking the influx of Ca^{2+} or blocking the Ca^{2+} priming component of cAMP synthesis. We assumed that activity of the inhibitory neuron transiently blocked further Ca^{2+} priming of cAMP synthesis in the sensory neuron, but not priming that results from Ca^{2+} present before the onset of activity of the inhibitory neuron. We also assumed that the inhibitory neuron had a burst-like property. The duration of activity in the inhibitory neuron was a function of the amount of time its input remained above threshold.[6] The output of the inhibitory neuron was constant during its activation.

The lateral inhibition network was implemented with the original single-cell model of the sensory neuron (see section 2 and Appendix). The addition of the inhibitory neurons did not impair the ability of the network to simulate the empirical data on nonassociative and associative plasticity. The thresholds of the inhibitory neurons were set above the strength of a CS2− cell, and below the strength of a CS1+. Consequently, only conditioned cells were capable of activating their inhibitory neurons and inducing lateral inhibition of the neighboring sensory neuron. The training paradigms were identical to those described for the original three-cell network (Figures 3 and 5).

[6] The duration of activity in the inhibitory neuron was equal to the time that the input remained above threshold multiplied by 15.

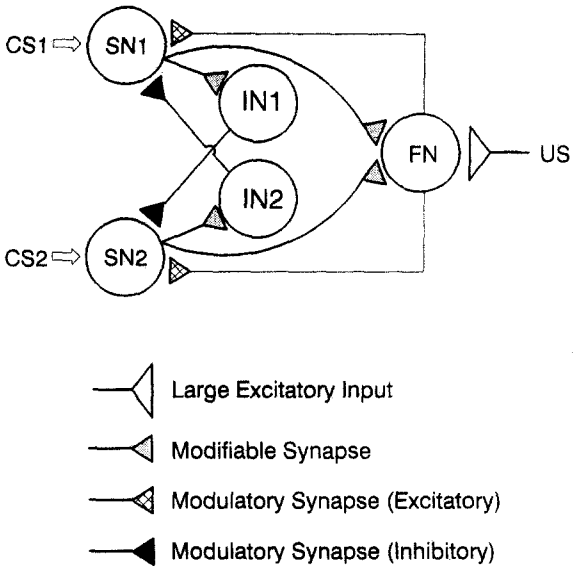

FIGURE 11. Sketch of the lateral inhibition-type network. The sensory neurons and facilitatory neuron are the same as were used in the simulations of the three-cell network with the original single-cell model. The inhibitory neurons (IN) are nonplastic elements that when active inhibit associative plasticity in the sensory neurons.

4.2 Simulations of Lateral Inhibition Network

As shown in Figures 12 and 13, the lateral inhibition network was capable of simulating both second-order conditioning and blocking. In contrast to the modified three-cell network, the lateral inhibition network was also able to quantitatively simulate the available empirical data on nonassociative and associative plasticity (Gingrich & Byrne, 1985, 1987).

Figure 12 illustrates the simulations of second-order conditioning which is achieved in a similar manner as in the previous networks (Figures 4 and 9). As a result of first-order conditioning (Figure 12a, Phase I), the CS1 cell is able to elicit activity in the facilitatory neuron and its inhibitory neuron (Figure 12b, Trial 5). Therefore, CS1 is able to function as reinforcing stimulus for the conditioning of the CS2 cell (Figure 12a, Phase II). During Phase II, the influx of Ca^{2+} into the CS2 cell occurs before onset of activity in inhibitory neuron 1. Therefore, second-order conditioning of the CS2 cell is not prevented by inhibitory neuron 1, because the associative plasticity observed in the CS2 cell results from the Ca^{2+} influx that occurred before the activation of inhibitory neuron 1 by the CS1 cell.

Figure 13a illustrates a simulation of blocking with the lateral inhibition network. At the end of Phase I, CS1 is able to activate both the facilitatory neuron and its inhibitory neuron (Figure 13b, Trial 5). As the compound CS1/CS2 presentations are paired with the US during Phase II, the CS1 cell activates its inhibitory neuron which in turn inhibits associative plasticity in the CS2 cell. Essentially, an inhibitory neuron detects that a CS cell has been conditioned, and inhibits associative plasticity in the other cell. A small degree of associative plasticity occurs in the CS2 cell, however, from the influx of Ca^{2+} that takes place during the brief time necessary for the CS1 cell to activate inhibitory neuron 1. The mechanism for blocking obtained with the lateral inhibition network is quite different from that of the three-cell network. Specifically, it does not rely on a shift in the time window of activation of the facilitatory neuron (although a shift does occur), but on the activation of an inhibitory neuron that blocks further associative plasticity. This lateral inhibition network is formally similar to a model previously described by Grossberg and Levine (1987).

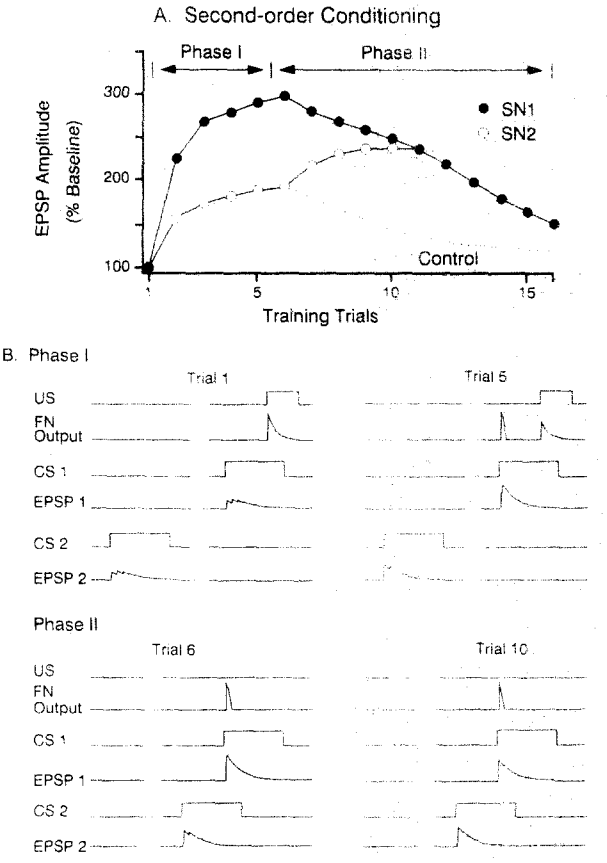

FIGURE 12. Simulation of second-order conditioning with the lateral inhibition network. (a) During first-order conditioning (Phase I, Trials 1–5), the CS1 cell exhibits first-order conditioning. During Phase II (Trials 6–15), the EPSPs produced by CS2 exhibit an increase in strength due to second-order conditioning. (b) The output of the sensory neurons and facilitatory neuron is similar to that depicted in Figure 4b. There are no significant differences between the output of this simulation and that of Figure 4 because, in contrast to the blocking paradigm, the influence of the inhibitory neurons is minimal in the second-order conditioning paradigm. Output of the inhibitory neurons are not shown. The threshold of both the facilitatory neuron and inhibitory neurons was 1050.

With the lateral inhibition network it was not necessary to have a large difference in strength between the CS1+ and CS2− cells. Furthermore, the constraints on the ISI functions and on the properties of the facilitatory neuron were less stringent. The lateral inhibition network demonstrates that it is theoretically possible for a network to simulate second-order conditioning and blocking even though the elements exhibit nonassociative enhancement and have a relatively modest difference between nonassociative and associative strength.

5. GENERAL DISCUSSION

The original single-cell model described by Gingrich and Byrne (1985, 1987), when implemented into the circuit suggested by Hawkins and Kandel (1984), can simulate either second-order conditioning or partial blocking, but not both with a single set of parameters. The key parameter is the threshold of the facilitatory neuron. To obtain both second-order conditioning and blocking with a three-cell network, we found that there must be at least a 100% difference in strength between the CS1+ and CS2− cells. This can be understood intuitively, since in order to obtain reasonable blocking, the facilitatory neuron must be able to distinguish between the control CS1−/CS2− and experimental CS1+/CS2− compound stimuli. If the threshold of the facilitatory neuron is between the strengths of the CS1−/CS2− and CS1+/CS2− compounds, it can make the distinction between a control and experimental blocking paradigm. To obtain second-order conditioning, however, the threshold of the facilitatory neuron has to be below the strength of the CS1+ cell. Thus, threshold must be above CS1−/CS2− strength and below CS1+ strength. It follows that if the connection of the CS1+ cell is not at least twice as strong as that of the CS2− cell, it is not possible to obtain both significant second-order conditioning and blocking. Thus, the original model of the sensory neuron when incorporated into a three-cell network was unable to perform reasonable simulations of blocking, in part, due to the constraints imposed by the empirical data in which the strength of a CS+ cell was not 100% greater than that of the CS− cell. Interestingly, most of the empirical data on associative neuronal plasticity in *Aplysia* have not shown increases of more than 100% in the strength of a CS+ cell in relation to a CS− cell (Buonomano & Byrne, 1990; Carew, Hawkins, Abrams & Kandel, 1984; Hawkins et al., 1983; Walters & Byrne, 1983). The same holds true for associative plasticity in the hippocampus (Gustafsson & Wigström, 1986; Kelso, Ganong & Brown, 1986; Larson & Lynch, 1986; Sastry, Goh & Auyeung, 1986). The importance of factors such as the magnitude of the change in associative strength in our simulations stress the point that if the purpose of a model is to provide insights into biological information processing and to test hypotheses on the mechanisms underlying learning, it may prove essential to maintain network parameters within physiological ranges.

An unexpected result of our simulations was that even though the three-cell network with the modified single-cell model neuron displayed a negatively accelerating acquisition function, it was able to simulate complete blocking with a three-cell network. As shown by Gluck and Thompson (1987), a difficult aspect of simulating complete blocking is that during Phase II, the CS2− cell should not undergo any associative plasticity, but the CS1+ cell must undergo associative plasticity in order to counterbalance extinction. There is an intrinsic difficulty in preventing the conditioning of the CS2− cell but not of the CS1+ cell with the three-cell network. Gluck and Thompson (1987), and Hawkins (1989a,b) have shown that in a system with a sigmoid acquisition curve, this difficulty can be overcome. With a sigmoid acquisition curve the rate of change of synaptic strength as a function of training is close to zero at both the initial (naive) phase of conditioning and at the asymptotic phase of training. Thus, both a trained CS1+ and a naive CS2− cell can receive small amounts of associative plasticity and maintain a steady-state strength. In contrast, a negatively accelerating acquisition function has different rates of change at its initial (maximal rate of change) and asymptotic phases (tending to zero). In order to obtain complete blocking with this type of acquisition curve, the CS2− cell can not undergo any associative plasticity, since its rate of change is much higher than that of the CS1+ cell. Otherwise, no matter how little associative plasticity the CS2− cell undergoes, it would eventually "catch up" to the CS1+ cell. Thus, there has to be a state-dependent process by which associative plasticity occurs in the CS+ cell, but not in the CS− cell. In our model this state-dependent plasticity emerges because the conditioned cell has a faster rate of influx of Ca^{2+}, due to broader spikes. Therefore, the CS+ cell can undergo associative plasticity within a time period ineffective for conditioning of the CS2− cell (see section 3.2). The finding that the modeled sensory neurons of the three-cell network exhibited state-dependent conditioning, which improved the simulations of blocking, was interesting since less detailed models do not capture this phenomenon. One of our initial objectives was to examine whether there are any qualitative differences among models that simulate neural processes at different levels of description. We found that a finer level of description may be important, because subtle properties of the network can emerge from the details of the subcellular processes.

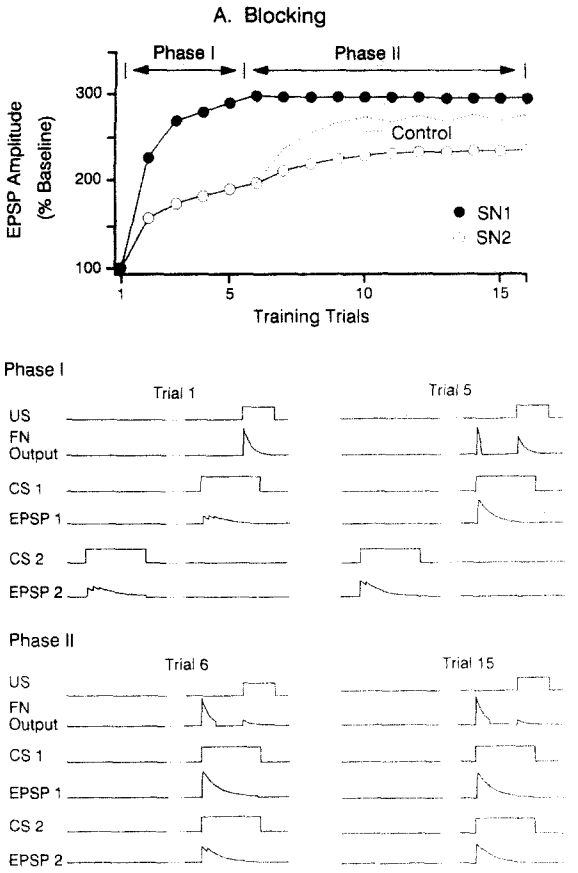

FIGURE 13. Simulation of blocking with the lateral inhibition network. (a) During Phase I, both the CS1 and CS2 cells exhibited the same degree of plasticity seen in the three-cell network with the original single-cell model (e.g., Figure 6a). During Phase II, the CS2 cell exhibited blocking. Although the CS2 cell exhibited some associative plasticity, it remained at an asymptote below that observed in the control paradigm (dotted line). (b) The activities of the elements are similar to those in Figure 6b, although, the EPSP produced by SN2 is not as enhanced in Trial 10. Blocking is achieved because during Phase II (Trial 6) the CS1 cell activated not only the facilitatory neuron but IN1, which blocked associative plasticity in the CS2 cell. IN traces are not shown. The threshold of both the facilitatory neuron and inhibitory neurons was 1050.

In contrast to previous models of classical conditioning that predict either a negatively accelerating or sigmoid acquisition function, our model can simulate both types of acquisition functions depending on the ISI. Behavioral data of classical conditioning in vertebrates also show that both sigmoid and negatively accelerating acquisition curves are observed during first-order conditioning depending on the ISI (Schneiderman & Gormezano, 1964; Schneiderman, 1966). It should be noted that our model as well as most models proposed to date address forms of classical conditioning in which the CR and UR are similar in nature and in which the functional ISIs are on the order of a few seconds. It will be of interest to see how well, if at all, the present models generalize to forms of classical conditioning in which the CR does not mimic the UR and/or those forms of classical conditioning in which ISIs on the order of hours can be effective.

The lateral inhibition network proved to be more robust than the three-cell network, in that it simulated second-order conditioning and blocking over a broader range of network parameters. For example, it was not necessary that the CS+ cell be twice as strong as a CS− cell. In the lateral inhibition network, blocking was achieved by a similar mechanism as in a model suggested by Grossberg and Levine (1987). CS representations compete among each other for reinforcement. Once the CS1 cell has been conditioned, it will inhibit plasticity in the naive CS2 cell, via lateral inhibition. In contrast to the three-cell network, the lateral inhibition network is capable of simulating second-order conditioning and blocking to a large extent as a result of circuit properties rather than by the specific construct of the elements. It appears that the features of the individual elements become less important as the number of circuit elements increases (see also Tesauro, 1988).

Previous work has shown that small neural networks composed of simple input–output functions and that utilize simple learning rules are able to simulate classical conditioning as well as some higher-order features of classical conditioning (Gluck & Thompson, 1987; Hawkins, 1989a,b; Klopf, 1988; Sutton & Barto, 1981, 1990). Here we extended these observations by showing that the same holds true when the construct of the elements better reflects the physiological properties of the actual neurons. However, it is clear from our simulations that in order for these networks to model second-order conditioning and blocking, certain specific constraints pertaining to the properties of the elements have to be satisfied. Ultimately, these constraints may be used for testing hypotheses for the mechanisms underlying associative learning. For example, one would predict that in order for the Hawkins and Kandel hypothesis to be biologically plausible there should be large increases in the strength of the CS+ cell and rapid accommodation (hundreds of milliseconds) of the facilitatory process.

A critical issue is how robust are these models. Will they continue to simulate second-order conditioning and blocking when simulations are performed with networks in which a large number of CS cells are present and any cell or combination thereof can be activated by a CS? It may appear that the type of networks addressed in this paper would not be able to account for these same features of associative learning when either a single cell or multiple cells can be activated by a CS since the thresholds of certain elements can play a critical role in the model. These networks, however, present an element of self-organization in that multiple compound CSs share the total CS strength. For example, in the modified

three-cell network, when conditioning a compound stimulus that consisted of two CSs, each CS asymptotes at approximately 50% of that observed when conditioning of a single CS. Thus, the strength of a CS is approximately the same independent of the number of cells activated by that CS. A necessary condition, however, is that there be a large difference in strength between a CS− and a CS+ cell, otherwise a small number of CS− cells can activate the facilitatory neuron.

Other higher-order features of conditioning such as contingency, conditioned inhibition, and some nuances of blocking, such as unblocking (Dickinson, Hall & Mackintosh, 1975), do not readily emerge from any of the above networks. Further assumptions would be necessary to account for these phenomena. Future questions that need to be addressed are whether these higher-order features of conditioning emerge from large network properties or from specific properties of individual neurons.

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APPENDIX

The equations used for the first (unmodified single-cell) model of this paper are presented below. For additional details see Figure 1 and Gingrich and Byrne (1985, 1987).

Dynamics of Ca^{2+}

$$I_{Ca} = A \cdot B \cdot K_C, \tag{A1}$$

$$A = 1 - \exp(-t_1/T_A), \tag{A2}$$

$$B = C \cdot \exp(-t_1/T_I), \tag{A3}$$

$$C = 1 - (1 - B') \cdot \exp(-t_2/T_R), \tag{A4}$$

$$F_{Ca} = K_D/(1 + M_I/C_{Ca}^2), \tag{A5}$$

$$F_{Ex} = C_{Ca} \cdot K_{VD}, \tag{A6}$$

$$\frac{dC_{Ca}}{dt} = \frac{(I_{Ca} - F_{Ca} - F_{Ex})}{V_C} \tag{A7}$$

Dynamics of Transmitter Mobilization

$$F_D = (C_S - C_R) \cdot K_{VD}, \tag{A8}$$

$$F_I = \frac{C_S}{C_{SI}}\left(\mathrm{PVM}_S + \frac{K_S}{1 + M_S/C_{Ca}^{Ns}}\right), \tag{A9}$$

$$\frac{d\mathrm{PVM}_S}{dt} = \left(\frac{K_S}{(1 + M_S/C_{Ca}^{Ns})} - \mathrm{PVM}_S\right) \cdot \frac{1}{T_S}, \tag{A10}$$

$$F_S = \frac{30}{1 + [200/(C_S - C_R)]}, \tag{A11}$$

$$F_{cAMP} = K_{EC} \cdot C_S \cdot C_{cAMP}, \tag{A12}$$

$$\frac{dC_R}{dt} = (F_{cAMP} + F_I + F_D - T_{CL}) \cdot (1/V_R), \tag{A13}$$

$$\frac{dC_S}{dt} = (F_S - F_I - F_D - F_{cAMP}) \cdot (1/V_S). \tag{A14}$$

Dynamics of cAMP

In the absence of activity in the FN:

$$\frac{dC_{cAMP}}{dt} = (-C_{cAMP}/T_{cAMP}) \tag{A15}$$

In the presence of activity in the FN:

$$\frac{dC_{cAMP}}{dt} = (-C_{cAMP}/T_{cAMP}) + K_{SC} \cdot Q + (K_{EC} \cdot C_{Ca} \cdot Q). \tag{A16}$$

Release of Transmitter

$$\text{Spike duration} = 0.003 + (K_{DC} \cdot C_{cAMP}). \tag{A17}$$

$$T_R = C_R \cdot V_R \cdot I_{Ca} \cdot K_R. \tag{A18}$$

Values and Definitions of Constants

C_{SI}	100	steady state value of C_S
K_C	103.0	constant for Ca^{2+} current
K_D	0.388	diffusion constant for Ca^{2+}
K_{DC}	$1.5 \cdot 10^{-5}$	constant for spike duration
K_{EC}	5360	constant for Ca^{2+}-dependent synthesis of cAMP
K_I	21.0	maximal rate of fast mobilization
K_{EC}	$2 \cdot 10^{-6}$	constant for cAMP-dependent mobilization
K_R	3.16	constant for transmitter release
K_S	35.0	maximal rate of slow mobilization
K_{SC}	1600	constant for Ca^{2+}-independent synthesis of cAMP
K_U	2907	constant for Ca^{2+} uptake
K_{VD}	0.001	constant for diffusion of transmitter
M_I	0.0008	concentration constant for fast mobilization
M_S	0.075	concentration constant for slow mobilization
M_U	790.0	concentration constant for Ca^{2+} uptake
Nf	2.83	Hill coefficient for fast mobilization
Ns	1.75	Hill coefficient for slow mobilization
T_A	0.001	time constant for activation of Ca^{2+} channel
T_{cAMP}	900	time constant of cAMP
T_I	0.44	time constant for inactivation of Ca^{2+} channel

T_R	15.6	time constant for recovery from inactivation of Ca^{2+} channel
T_S	213.0	time constant for slow mobilization
V_I	2.15	volume of Ca^{2+} compartment
V_R	1.0	volume of releasable pool
V_S	6.08	volume of storage pool

Initial Values and Definitions of Variables

A	0	activation of Ca^{2+} channel
B	1	inactivation of Ca^{2+} channel during spike
B'	1	value of B at end of a spike
C	1	recovery from inactivation of Ca^{2+} channel
C_{Ca}	0	concentration of Ca^{2+}
C_{cAMP}	0	concentration of cAMP
C_R	100	concentration of transmitter in releasable pool
C_S	100	concentration of transmitter in storage pool
F_C	0	Ca^{2+}-dependent mobilization
FcAMP	0	cAMP-dependent mobilization
F_D	0	diffusion of transmitter
F_{DC}	0	diffusion of Ca^{2+}
F_N	0	synthesis of transmitter
F_U	0	uptake of Ca^{2+}
I_{Ca}	0	Ca^{2+} current
PVM_S	0	potential for mobilization
Q	1	accommodation of facilitatory neuron
t_1	0	time after beginning of spike
t_2	0	time after last spike
T_R	0	release of transmitter

All time constants are given in seconds.