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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Between October 1, 1990 and September 30, 1991, progress was made in six areas. First, voltage-clamp experiments investigated the modulation of the voltage-dependent K^+ current ($I_{K,V}$) by serotonin (5-HT). Second, a computer program that is a general-purpose Simulator for Neural Networks and Action Potentials (SNNAP) was developed. Third, extensions were made to the single-cell model of associative learning by incorporating Hodgkin-Huxley type membrane currents, descriptions of the modulation of membrane currents by 5-HT, and a model of intracellular Ca^{2+} diffusion. Fourth, SNNAP was used to investigate the role of interneurons in determining the intensity and duration of motor neuron responses that mediate the tail-withdrawal reflex. Fifth, experiments characterized the synaptic interactions among the neurons of a central pattern generator (CPG) that underlies aspects of feeding behavior. Sixth, SNNAP was used to begin simulating the neurons and synaptic connections of the feeding CPG. In addition, work on the model of the bursting neuron R15 was completed.

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Annual Technical Report

Grant Number: AFOSR-91-0027

Grant Title: Analysis and Synthesis of
Adaptive Neural Elements and Assembles

Period of Report: 1 October, 1990 - 30 September, 1991

I. Summary

The overall objectives of this research are to analyze the properties of identified neurons and neural networks in *Aplysia* that exhibit nonassociative and associative plasticity and to examine the role of neuronal plasticity in learning and memory. Two interrelated approaches are used, one empirical and the other modeling. Between October 1, 1990 and September 30, 1991, progress was made in six areas, which directly address the Specific Aims set forth in AFOSR-91-0027. First, voltage-clamp experiments investigated the modulation of the voltage-dependent K^+ current ($I_{K,V}$) by serotonin (5-HT). Second, a computer program that is a general-purpose Simulator for Neural Networks and Action Potentials (SNNAP) was developed. Third, extensions were made to the single-cell model of associative learning by incorporating Hodgkin-Huxley type descriptions of membrane currents, quantitative descriptions of the modulation of membrane currents by 5-HT, and a shell model of intracellular Ca^{2+} diffusion. Fourth, SNNAP was used to investigate the role of interneurons in determining the intensity and duration of motor neuron responses that mediate the tail-withdrawal reflex. Fifth, experiments characterized the synaptic interactions among the neurons of a central pattern generator (CPG) that underlies aspects of feeding behavior. Sixth, SNNAP was used to begin simulating the neurons and synaptic connections of the feeding CPG. In addition, work on the model of the bursting neuron R15 was completed.

II. Research Objectives

The research supported by AFOSR-91-0027 has seven Specific Aims:

1. Conduct a detailed Hodgkin-Huxley type analysis of the membrane currents of sensory neurons and determine how the parameters governing these membrane currents are modulated by facilitatory (e.g., 5-HT) and inhibitory (e.g., FMRFamide) transmitters and/or neural pathways.

2. Quantitatively analyze the discharge properties of the modulatory interneurons in response to intracellular depolarizing current pulses (to gain insights into their intrinsic biophysical properties) and in response to reinforcing stimuli (to gain insight into the way by which they are activated physiologically).

3. Incorporate as much empirical data as is available into the biologically derived single-cell model of learning.

4. Examine the ability of the neural circuit that mediates the tail-withdrawal reflex to support forms of associative plasticity that are analogous to higher-order features of classical conditioning, such as second-order conditioning and blocking.

5. Incorporate as much empirical data as is available into our neural-network models for higher-order features of classical conditioning.

6. Develop a neuronal analogue of operant conditioning using identified neurons that are components of the central pattern generator (CPG) controlling feeding behavior.

7. Incorporate as much empirical data as is available into a biologically derived neural-network model for operant conditioning.

III. Status of Research (Progress Report)

A. Voltage-Clamp Analysis of the Serotonergic Modulation of the Voltage-Dependent Potassium Current ($I_{K,V}$) in Tail Sensory Neurons of *Aplysia*

The serotonergic modulation of membrane currents is an important mechanism contributing to presynaptic facilitation of transmitter release from sensory neurons, which in turn, is thought to be a cellular mechanism contributing to several simple forms of learning. Previous analyses of the biophysical mechanisms of plasticity in the sensory neurons of *Aplysia* have focused on a serotonin (5-HT)-sensitive K^+ current, which is termed the S current ($I_{K,S}$). We recently demonstrated that 5-HT also modulates a highly voltage-dependent K^+ current ($I_{K,V}$) (Baxter and Byrne, *J Neurophysiol*, **62**: 665-679, 1989). We have extended these observations by quantitatively examining the effects of 5-HT on $I_{K,V}$. A Hodgkin-Huxley type model and curve fitting techniques were used to determine the parameters describing the activation and inactivation kinetics and the magnitude of $I_{K,V}$. Application of 5-HT decreased the magnitude of $I_{K,V}$ by about 50%. In addition, 5-HT increased the activation and inactivation time constants of $I_{K,V}$ by about 25% and 100%, respectively.

Thus, serotonergic modulation appears to both slow the kinetics and reduce the magnitude of $I_{K,V}$. In order to examine how this modulation of $I_{K,V}$ contributes to 5-HT-induced changes in the electrophysiological properties of sensory neurons, these experimental observations are being incorporated into a single-cell model of a sensory neuron (see below).

B. Simulator for Neural Networks and Action Potentials (SNNAP)

We have developed a computer program that is a general-purpose Simulator for Neural Networks and Action Potentials (SNNAP). Some of the general features and capabilities of SNNAP include:

1. The intrinsic voltage-dependent membrane currents of individual neurons are described as an equivalent electrical circuit with Hodgkin-Huxley type descriptions of individual ionic currents. Each neuron may include up to 20 different ionic conductances. Each conductance is described by a set of first-order ordinary differential equations (ODEs) for activation and inactivation with voltage-dependent steady-state values and time constants. Thus, SNNAP can realistically and quantitatively simulate the distinctive electrical properties of individual neurons.

2. The parameters that define the electrical properties of a neuron are contained in a cell-parameter file. Each neuron has its own file. Thus, the user can develop a library of cell-parameter files that designate individual neurons, each with unique properties.

3. SNNAP is capable of simulating a network of up to 20 fully connected neurons. Connections among neurons can be made by either electrical or chemical synapses. Chemical synapses are simulated by the numerical solution of a second-order ODE driven by a pulse equal to the duration of the presynaptic action potential. Using this solution, the postsynaptic cell can respond to changes in the duration of a presynaptic action potential. Moreover, postsynaptic potentials from successive presynaptic action potentials summate in real time. Thus, SNNAP can simulate a variety of synaptic connections and forms of synaptic plasticity.

4. The parameters that define the patterns of connectivity among neurons in a neural network are contained in a gobal-parameter file. Each network has its own file. Thus, the user can develop a library of gobal-parameter files

that designate individual networks, each with unique combinations of neurons and patterns of connectivity.

5. SNNAP generates a screen display that plots the membrane voltage vs. time for one or more of the neurons in the network. The user specifies which and how many neurons are included in the display and the scaling of each trace. SNNAP also can create data files that include all of the state variables for each neuron, which are generated during a simulation. Hard copies of the screen display can be generated with either a laser printer or a pen plotter. In addition, the data files can be imported into other commercially available programs, such as Lotus 123.

SNNAP is easy to use and versatile, yet it is realistic and quantitative. Thus, we believe that SNNAP can be applied to a wide range of research projects that simulate the electrical activity of neurons and neural networks.

C. Simulations of Action Potentials, Transmitter Release, and Plasticity of Sensorimotor Synapses in *Aplysia*

We have begun to extend our single-cell model of associative learning by incorporating more realistic descriptions of the biophysical, biochemical and electrophysiological properties of sensory neurons. A Hodgkin-Huxley type membrane model of an *Aplysia* sensory neuron has been combined with a model of transmitter mobilization and release, as well as a model of the synaptic coupling with a follower motor neuron. The membrane currents in the model, as well as their modulation 5-HT, were largely based on voltage-clamp data from the sensory neuron soma (see above). In addition, material balances on cAMP and Ca^{2+} in the terminal were included. Release was modeled as a cubic function of Ca^{2+} current and a linear function of available transmitter. The population of transmitter vesicles was compartmentalized into pools. In addition to its effects on membrane currents, a facilitatory effect of 5-HT on transmitter mobilization was modeled. The parameters of the transmitter mobilization and release model were adjusted by fitting the simulated excitatory postsynaptic potential (EPSP) to published data recorded during presynaptic voltage-clamp pulses of varying duration (Hochner et al., *Proc Natl Acad Sci USA*, **83**: 235-240, 1989). The model of synaptic coupling included transmitter accumulation and removal from the cleft, as well as kinetics associated with the transmitter-gated current in the postsynaptic membrane. Simulations of voltage-clamped sensory neurons

produced a good fit to the waveforms and maximum amplitudes of EPSPs under normal, depressed and facilitated conditions. Simulations of action potentials also accurately predicted the resultant spike-induced EPSP. Moreover, modulation of K^+ currents and mobilization simulated empirically observed 5-HT-induced spike broadening and enhancement of transmitter release. The goal is to incorporated this model of a sensory neuron and its synaptic terminal into a realistic network (see below) in order to simulate the modifications of reflex circuits by simple forms of learning.

D. A Network Model of the Tail-Withdrawal Circuit in *Aplysia*

The tail-withdrawal reflex is mediated, at least in part, by a monosynaptic circuit consisting of sensory neurons and motor neurons. The strength of the connection between the sensory and motor neurons is modulated by several forms learning. Although the relationship between the magnitude of this monosynaptic connection and the magnitude of the reflex response is understood, little is known about the determinants of response duration in motor neurons. For example, it is difficult to explain how brief (<1 s) trains of monosynaptic EPSPs evoked in motor neurons by activity in sensory neurons can drive extended (>10 s) activity in motor neurons and how observed changes in the amplitudes of these EPSPs produce changes in the duration of motor neurons responses. To examine quantitatively the determinants of the conversion of stimulus intensity into the duration of motor neuron responses, SNNAP was used to construct a computer model representing the interactions among neurons of the tail-withdrawal circuit. Membrane conductances of model neurons are described by Hodgkin-Huxley type equations. Parameters were derived from electrophysiological and, in some cases, voltage-clamp studies (see above).

Simulations indicate that monosynaptic connections from a number of sensory neurons to a single motor neuron contribute only to the first 600 ms of the motor neuron response, even when synaptic efficacies are greatly enhanced. In order to simulate long-duration motor neuron responses, it is necessary to include elements representing recently described excitatory interneurons that elicit slow, decreased-conductance EPSPs in motor neurons (Cleary and Byrne, *Soc Neurosci Abstr*, **11**: 692, 1985, manuscript in preparation). Disynaptic connections via as few as two interneurons can lead to extended (about 20 s) response durations in motor neurons at average spike rates of about 2 spikes/second. Furthermore, the polysynaptic circuit simulates empirically

observed neural plasticity in both the magnitude and duration of the motor neuron response. Enhancement by 100% of the amplitudes of the synaptic connections from sensory neurons leads to an 85% increase in the number of spikes fired by the motor neuron and a 25% increase in the duration of the motor neuron response. Augmentation of the connections from interneurons to the motor neuron has effects very similar to those of enhancement of connections from sensory neurons. The circuit can account for the effects of enhancement of depressed synapses as well. Effects of plasticity in sensory neurons and interneurons are cumulative. In conclusion, interneurons evoking slow PSPs can transform information regarding stimulus intensity into the duration of a response. The gain of the amplitude-to-duration conversion is adjustable via physiologically realistic synaptic modulation. We predict that changes in the synaptic connections from sensory neurons to interneurons and from interneurons to motor neurons accompany modulation of the tail-withdrawal response and simple forms of learning. Moreover, these simulations provide general insights into information processing in the nervous system by illustrating mechanisms for intensity to duration conversion.

E. Synaptic Interactions Among Pattern Generating Neurons in Buccal Ganglia of *Aplysia*

As a first step toward investigating the cellular mechanisms of operant conditioning, we have begun to identify elements of the circuit that mediate feeding behavior. Several neurons in the buccal ganglia have been identified that are members of a central pattern generator (CPG) controlling aspects of feeding. Susswein and Byrne (*J Neurosci*, **8**: 2049-2061, 1988) identified cells B31/32 and B35 on the caudal surface of the buccal ganglia, and Plummer and Kirk (*J Neurophysiol*, **63**: 539-558, 1990) identified cells B51 and B52 on the rostral surface. To further examine how these neurons might function as a CPG, we have characterized the synaptic interactions among B31/32, B35, B51 and B52.

Simultaneous intracellular recordings were made from either B31/32 or B35 on the caudal surface of the left buccal ganglion and from B51 and/or B52 on the rostral surface of the right buccal ganglion. Intracellular stimulation of B51 elicited inhibitory postsynaptic potentials (IPSPs) in B31/32. This input was blocked by high divalent saline, suggesting that it was polysynaptic. Similarly, stimulation of B51 elicited IPSPs in B35, which appeared to be polysynaptic. Intracellular stimulation of B52 elicited discrete, short-latency, one-for-one IPSPs

in B35 and B51, suggesting that these connections were monosynaptic. In contrast, stimulation of B52 never affected the membrane potential of B31/32. Intracellular stimulation of B31/32 elicited only IPSPs in B51, whereas activity in B31/32 elicited a mixture of IPSPs and EPSPs in B52. Stimulation of B35 produced monosynaptic EPSPs in B52 and polysynaptic IPSPs in B51. As previously reported, it was observed that B51 and B52 reciprocally inhibited each other and that B35 excited B31/32. In addition, recordings were made from these neurons during patterned activity. Activity in B52 coincided with activity in B31/32, whereas activity in B51 occurred while B31/32 and B52 were inhibited.

This pattern of connectivity is only one of the factors determining how this neural circuit may function as a CPG. Additional factors, such as the intrinsic properties of the neurons, also must be considered. Currently, the simulation program SNNAP is being used to construct a model representing the properties and interconnections of these identified neurons, and to examine how this neural circuit may function as a CPG (see below).

F. Simulations of the Neurons and Synaptic Connections of the Feeding CPG

SNNAP is being used to simulate elements of a CPG in the buccal ganglia of *Aplysia* to understand the mechanisms that produce and modify patterned neuronal activity. As a first step, the intrinsic properties of cell B51 and B52 were simulated, including the delayed response and regenerative properties of B51 and postinhibitory rebound in B52. Next, chemical synaptic connections between B51 and B52 (see above) were simulated to determine whether this two-cell circuit was sufficient to generate the pattern described by Susswein and Byrne (*J Neurosci*, **8**: 2049-2061, 1988). A depolarizing current pulse in the simulated B52 produced a burst of spikes that led to a barrage of summating IPSPs in B51. The simulation resembles empirical data (Baxter and Byrne, *Soc Neurosci Abstr*, **17**: 124, 1991). A depolarizing current in B51 led to inhibition and subsequent spiking (postinhibitory rebound) in B52, which also resembles empirical data. Depolarization of <u>both</u> cells only led to inhibition in B51. B51 did not fire because the predominate inhibition produced by B52 hyperpolarized B51 before the depolarizing current pulse could drive B51 to threshold. Thus, depolarization of neither one nor both of the cells led to the patterned activity typically observed in the buccal ganglia. These simulations indicate that

additional elements, such as neurons B31/32, must be included in the circuit to more fully account for the function of the CPG.

G. Simulation of the Bursting Activity of Neuron R15 in *Aplysia*: Role of Ionic Currents, Calcium Balance, and Modulatory Transmitters

The development of a Hodgkin-Huxley type model of R15 was completed. This model more accurately reflects the known properties of R15 (Canavier et al., *J Neurophysiol*, **66**: 2107-2124, 1991) by incorporating two significant improvements over previous models of R15. First, the single-neuron model incorporates quantitative and realistic descriptions of most of the membrane currents that are know to exist in the somata of R15. All available published experimental data on R15 has been utilized. Thus, the model simulates the actual magnitudes and time courses of the individual currents. Second, the model incorporates a fluid compartment that provides for a Ca^{2+} balance within the cell. The intracellular levels of Ca^{2+} play critical roles in a number of processes in R15, such as modulating membrane currents and modulating the activity of second-messenger and enzymatic systems. The model can simulate the actual magnitudes and time courses of fluctuations in intracellular Ca^{2+} that have been observed experimentally. Thus, the model can be used to simulate and to examine a wide range of electrochemical activities in R15 and provides general insights into the generation of rhythmic neuronal activity.

The model predicts many features of the activity of bursting neurons, including transitions between an endogenous bursting mode, a silent mode, and a beating mode as a function of applied current. The model has provided insights into the ability of bursting neurons to exhibit different modes of activity and which parameters are critical for determining the characteristics of bursting activity. In addition, preliminary results indicate that the single-neuron model can be used to examine the effects of neuromodulators on electrically activity. Based on the simulations it appears that there are potentially novel mechanisms with which modulatory agents can exert their effects on rhythmic neuronal activity.

IV. Publications

A. Abstracts

1. Baxter, D.A. and Byrne, J.H. Synaptic interactions among pattern generating neurons in buccal ganglia of *Aplysia*. *Society for Neuroscience Abstract*, **17**: 124, 1991.

2. Canavier, C.C., Baxter, D.A., Clark, J.W. and Byrne, J.H. Simulations of action potentials, transmitter release, and plasticity of sensorimotor synapses in *Aplysia*. *Society for Neuroscience Abstract*, **17**: 1590, 1991.

3. White, J.A., Cleary, L.J., Ziv, I. and Byrne, J.H. A network model of the tail-withdrawal circuit in *Aplysia*. *Society for Neuroscience Abstract*, **17**: 1590, 1991.

4. Ziv, I., Baxter, D.A. and Byrne, J.H. Simulator for neural networks and action potentials (SNNAP): application to a central pattern generator. *Society for Neuroscience Abstract*, **17**: 125, 1991.

B. Articles

1. Baxter, D.A. and Byrne, J.H. Ionic conductance mechanisms contributing to the intrinsic electrophysiological properties of neurons. *Current Opinion in Neurobiology*, **1**: 105-112, 1991.

2. Canavier, C.C., Clark, J.W. and Byrne, J.H. Simulation of the bursting activity of neuron R15 in *Aplysia*: role of ionic currents, calcium balance, and modulatory transmitters. *Journal of Neurophysiology*, **66**: 2107-2124, 1991.

3. Raymond, J.L., Baxter, D.A., Buonomano, D.V. and Byrne, J.H. A learning rule based on empirically-derived activity-dependent neuromodulation supports operant conditioning in a small network. *Neural Networks*, in press, 1992.

C. Chapters

1. Byrne, J.H. and Crow, T. Examples of mechanistic analyses of learning and memory in invertebrates. In: J.L. Martinez, Jr. and R.P. Kesner (Eds.),

Learning and Memory: A Biological View (pp. 329-358). New York: Academic Press, Inc., 1991.

D. Manuscripts in Preparation or Under Review

1. Baxter, D.A. and Byrne, J.H. Learning rules in neurobiology. To appear in D. Gardner (Ed.), *The Neurobiology of Neural Networks* (in preparation). Cambridge: MIT Press/Bradford Books, 1992.

2. Canavier, C.C., Baxter, D.A., Clark, J.W. and Byrne, J.H. Simulation of action potentials, excitability, and the effects of serotonin on sensory neurons in *Aplysia*. In preparation, 1992.

3. White, J.A., Baxter, D.A. and Byrne, J.H. Serotonin modulates the kinetics and magnitude of the voltage-dependent potassium current in tail sensory neurons of *Aplysia*. In preparation, 1992.

V. Professional Personnel

Baxter, Douglas A., Ph.D.

Byrne, John H., Ph.D.

Canavier, Carmen C., Ph.D.

Sorenson, Jeffrey M., Medical Student

White, John A., Ph.D.

Ziv, Israel, Ph.D.

VI. Interactions: Presentations to Professional Organizations, Special Meetings, and Invited Lectures

A. Presentations to Professional Organizations

1. 20th Annual Meeting of the Society for Neuroscience

Dr. Baxter presented the abstract entitled "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in

Aplysia" at the 20th Annual Meeting of the Society for Neuroscience on November 2, 1990.

2. 35th Annual Meeting of the Biophysical Society

Dr. Canavier was a participant in the Biophysical Society Workshop on Chaos Dynamics in Biophysics on Febrary 27, 1991, where she summarized some aspects of AFOSR-sponsored research.

3. Annual Meeting of the American Association of Anatomists

Dr. Byrne gave a lecture entitled "Recent Advances in the Analysis of Learning" on April 22, 1991, which summarized aspects of AFOSR-sponsored research.

B. Presentations to Special Meetings

1. 1990 Meeting on Cellular and Molecular Neurobiology of *Aplysia*

Two abstracts, which summarized aspects of AFOSR-sponsored research, were presented at the Meeting on Cellular and Molecular Neurobiology of *Aplysia* on October 7, 1990. Dr. Baxter presented an abstract entitled "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in *Aplysia*". Miss Raymond presented an abstract entitled "Activity-dependent neuromodulation can support operant conditioning in a small oscillatory network".

2. Society for Neuroscience Short Course on Neural Computations

Dr. Byrne was one of six guest lectures who traveled to Mexico City on May 2 and 3 to participant in the Mid-Year Short Course "Neural Computations" sponsored by FIDIA Research Foundation and the Society for Neuroscience. During his lecture, Dr. Byrne presented results form AFOSR-sponsored research.

3. Gordon Conference

Dr. Byrne participated in the Gordon Conference on "Regulation of Synaptic Activity" on June 17-21. During his lecture, Dr. Byrne presented results of AFOSR-sponsored research.

4. Cold Spring Harbor Laboratory Courses

As a faculty member, Dr. Byrne presented aspects of AFOSR-sponsored research during the Cold Spring Harbor Laboratory Course entitled "Cellular and Molecular Biology of Learning and Memory" on July 14-28, 1991.

5. Dahlem Workshop

Dr. Byrne participated in the Dahlem Workshop in Berlin on "Exploring Brain Function: Models in Neuroscience" on September 29, 1991 to October 5, 1991. During his lecture, Dr. Byrne presented results of AFOSR-sponsored research.

C. Invited Lectures

1. "Neural and Molecular Basis of Long-Term Sensitization in *Aplysia*" This lecture was presented by Dr. Byrne at the 1990 Meeting on Cellular and Molecular Neurobiology of *Aplysia* on October 6, 1990.

2. "Aspects of the Neural and Molecular Mechanisms of Short-Term Sensitization in *Aplysia*" This lecture was presented by Dr. Byrne to the Department of Zoology at The University of Texas at Austin on March 7, 1991.

3. "Experimental and Modeling Approaches to Neural and Network Determinants of Learning" and "Neural and Molecular Mechanisms Underlying Short-Term and Long-Term Sensitization" These two lectures were presented by Dr. Byrne to the Computational Neuroscience Program at Case Western on April 9-10, 1991.

4. "Serotonergic Modulation of Potassium Currents in Tail Sensory Neurons of *Aplysia*" This lecture was presented by Dr. Baxter to the Department of Zoology at The University of Texas at Austin on April 24, 1991.

VII. New Discoveries, Inventions or Patent Disclosures

We are currently working with the Office of Technology Management (OTM) at The University of Texas Health Science Center (UTHSC) at Houston to

adequately copyright, register, and licence the computer program SNNAP that was developed during AFOSR-sponsored research.

VIII. Additional Clarifying Information

Not Applicable.