COMPUTER SIMULATION OF AFTER-INHIBITION IN CRAYFISH SLOWLY ADAPTING STRETCH RECEPTOR NEURON

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ABSTRACT A theoretical model is described which is able to mimic the responses of slowly adapting stretch receptor neurons of crayfish to applied currents. Its principal feature is postspike inhibition, in which each nerve impulses produces a small inhibitory current that decays with a simple exponential time-course that is long compared with normal interspike intervals. The model was simulated with both an analogue and a digital computer. Parameters for particular model neurons were determined both by an analysis of experimental data obtained from adaptation to constant injected currents, and by matching computer output to the data. Parameter values estimated by the two techniques agreed within ±10%. Model parameters determined from adaptation data successfully predicted the magnitude and time-course of posttetanic hyperpolarization (PTH) in the stretch receptor neuron. In addition, model neurons were able to reproduce posttetanic depression (PTD) as seen in stretch receptor cells.

INTRODUCTION

As in many other "tonic" nerve cells, the slowly adapting stretch receptor neuron of crayfish shows adaptation in response to a constant depolarizing current: the firing rate is high at the onset of the current, but soon declines to a steady-state value which depends on the current intensity (Nakajima and Onodera, 1969; Sokolove and Cooke, 1971). In addition, this cell shows inhibition of spiking after a rapid train of impulses, by an amount which is approximately proportional to the number of impulses in the train (Sokolove and Cooke, 1971). Both DC adaptation and posttetanic depression (PTD) were shown to result from the action of a hyperpolarizing electrogenic pump activated by the Na^+ entering with each impulse (Sokolove and Cooke, 1971).

Here I provide a general theoretical framework for predicting the frequency re-

sponse, not only of the tonic stretch receptor, but also of any tonic neuron showing DC adaptation and PTD, independent of the mechanism involved. For example, DC adaptation in the *Limulus* eye eccentric cell (Fuortes and Poggio, 1963; Stevens, 1964; Purple and Dodge, 1966; Lange et al., 1966) has been attributed to "self-inhibition": each outgoing spike produces an inhibitory postsynaptic potential (IPSP) in the same cell via an axon collateral (Stevens, 1964; Purple and Dodge, 1966).

I propose the term "after-inhibition" for any situation in which each nerve impulse is followed by a period of inhibition (i.e., of increased threshold) longer than can be accounted for by spike refractoriness. Regardless of the mechanism underlying after-inhibition, e.g. an electrogenic pump or an IPSP, the neuron demonstrates DC adaptation and PTD of ongoing activity.

An earlier theoretical treatment of self-inhibition by Stevens (1964) successfully described adaptation to a constant current in the *Limulus* eye eccentric cell. In this paper I follow the same basic approach to obtain more general mathematical expressions for after-inhibition. In contrast to the Stevens treatment, however, it is assumed here that both excitation and inhibition are caused by *currents* instead of potentials. The theoretical results are then applied to the slowly adapting stretch receptor neuron using both analogue and digital computers to simulate the response of the cell to depolarizing currents and to trains of antidromic impulses. In addition, certain parameters in the after-inhibition model are shown to have a physical significance with regard to electrogenic sodium pumping and spike initiation in the stretch receptor cell.

THEORY

Basic Assumptions

Stevens (1964) assumed that firing in a nerve cell is the result of the interaction of excitatory and inhibitory *potentials*. Two factors argue against this model in the case of the tonic stretch receptor cell: first, the firing rate of this neuron depends in a linear fashion on depolarizing *current* (Wendler and Burkhardt, 1961; Terzuolo and Washizu, 1962; Sokolove and Cooke, 1971). This relationship has been found in other tonic neurons as well (Fuortes and Mantegazzini, 1962; Fuortes and Poggio, 1963; Granit et al., 1963; Chapman, 1966). Secondly, the current-determined model allows the direct estimation of certain parameters related to electrogenic sodium pumping (see Discussion).

The initial assumption is that the instantaneous firing frequency f is proportional to the difference between an excitatory current G and an inhibitory current J:

$$f = k(G - J). \tag{1}$$

The instantaneous frequency f is commonly defined as the inverse of the time

interval between successive nerve impulses. In the present treatment I assume that this is equivalent to a "smeared" continuous rate function, $f(t)$ = number of impulses per unit time at time t. In general the assumption is valid as long as G and J vary slowly compared with the time between impulses.

The second basic assumption is that the inhibitory current is incremented by each impulse produced, and that it decays exponentially. Thus,

$$dJ/dt = b'f - (1/\tau)J, \tag{2}$$

where the constant b' is the incremental inhibitory current per impulse and τ is the time constant of the decay of inhibitory current. Table I summarizes the parameters and their units.

Solution for a Constant Current Step

By differentiating equation 1 and combining with equation 2 to eliminate terms containing J and its derivative, we have

$$\left(\frac{1 + bk}{k}\right)f + \frac{\tau}{k}\frac{df}{dt} = G + \tau\frac{dG}{dt}, \tag{3}$$

where $b = b'\tau$. For a constant excitatory current, $dG/dt = 0$. Letting $a = \tau/(1 + bk)$ equation 3 becomes

$$f + a\frac{df}{dt} = \frac{k}{\tau}aG. \tag{4}$$

Integrating we get

$$f(t) = \frac{kGa}{\tau}(1 - e^{-t/a}) + Ce^{-t/a}, \tag{5a}$$

TABLE I

DEFINITIONS AND UNITS OF PARAMETERS OF THE CURRENT-DETERMINED AFTER-INHIBITION MODEL

Parameter	Definition	Units
f	Instantaneous firing frequency (defined as the inverse of the time between spikes)	sec^{-1}
G	Applied excitatory current	namp
J	Total inhibitory current resulting from impulse discharge	namp
k	Proportionality constant between frequency and current (slope of the plot of initial frequency vs. applied current)	$namp^{-1}$ sec^{-1}
b'	Inhibitory current from a single nerve impulse	namp
τ	Time constant for the decay of inhibitory current after an impulse	sec
b	$= b'\tau$ (approximately the ratio of inhibitory current to frequency when firing rate is steady)	namp sec

where C depends on initial conditions. In the case of a cell which has been quiet for a long time ($\gg\tau$) before the constant current at $t = 0$, we can set $J = 0$ in equation 1. Thus,

$$f(0) = C = kG. \tag{5 b}$$

Combining and rearranging gives

$$f(t) = kG\left\{\frac{1}{1+bk} + \left(1 - \frac{1}{1+bk}\right)e^{-t(1+bk)/\tau}\right\}. \tag{6}$$

This is the solution for the case of a constant current step and is *not* the same as that reported earlier (Stevens, 1964, p. 47), although the conclusions which follow are indeed similar. Two observations can be made immediately:

(*a*) The initial frequency decays from an initial value of kG when $t = 0$ to an asymptotic value of $kG/(1 + bk)$ as $t \to \infty$. Thus

$$\frac{f(0)}{f(\infty)} = \frac{kG}{kG/(1+bk)} = 1 + bk. \tag{7}$$

(*b*) The decay constant of the frequency response,

$$\tau_f = \frac{\tau}{1+bk}, \tag{8}$$

is smaller than the inhibitory decay constant (τ). Relations 7 and 8 are especially useful when relating experimental data to the model.

METHODS

Analogue Computer Simulation

While the solution of equation 3 for a constant excitatory current may be obtained analytically, one would also like to examine the behavior of the model for arbitrary $G(t)$. Therefore, an analogue computer (Electronics Associates, Inc., Long Branch, N. J., 680) was programmed for the simultaneous solution of equations 1 and 2. An x-y plotter driven by the computer was used to display $f(t)$, $G(t)$, and $J(t)$ for further examination and comparison with data from experiments on the tonic stretch receptor neurons (see below). Potentiometers which controlled the values of τ, b', and k were set manually and their settings recorded for each run.

Digital Computer Simulation

Although the analogue model was sufficient to obtain a "smooth" frequency function $f(t)$, in some cases accurate knowledge of successive interspike intervals was required (i.e., when modeling PTD). Therefore, a program was written for an IBM 1620 computer which was similar to one described earlier for use in modeling lateral inhibition in *Limulus* eye (Lange et al., 1966, p. 439–442).

The basic elements of the program are as follows.

(*a*) An effective stimulus current S is formed from the difference between the excitatory (generator) current G and the inhibitory current J:

$$S = (G - J). \tag{9}$$

(*b*) Impulses are generated when $\int S\mathrm{d}t$ attains a threshold value A ($=1/k$). The integral is approximated by a running sum with a 1 msec time step. After an "impulse" the sum is reset to zero. Thus, an interspike interval of Δt is generated when:

$$A = \int_0^{\Delta t} S\mathrm{d}t = \int_0^{\Delta t} (G - J)\,\mathrm{d}t. \tag{10}$$

(*c*) At the time of occurrence of each impulse, J is increased (so that S is decreased) by a small amount b'. During successive clock cycles, J is decreased in an exponential fashion with a decay constant τ (i.e. J is multiplied by the constant $e^{-\delta/\tau}$ where δ is the time step, usually fixed at 1 msec).

(*d*) In the course of preliminary studies it was found that in order to mimic the behavior of real neurons it was necessary to limit the value of the integral in equation 10 to positive values. Thus, in the event that S was negative ($J > G$), the running sum was not incremented until S once again became positive (because of decay of J or increase of G).

Equation 10 is formally equivalent to charging a capacitor from a current source (S has units of current and A is the charge accumulated in Δt) and this last condition is analogous to inserting a diode in series with the capacitor. Thus, inhibitory or "negative" currents (J) can reduce excitatory or "positive" currents (G), but cannot reverse the polarity on the capacitor.

The justifying reasons for this restraint are not completely apparent at present; however, one can envision a physical model in which the "charging capacitor" corresponds to a distribution of *ion-specific sites* on the interior of a rectifying membrane at the spike-initiating zone. Positive (depolarizing) currents would lead to an accumulation of charge (Na^+?) at these sites, and when a critical charge density was reached a spike would be triggered. During the spike the accumulated charge would be dissipated. Presumably, then, negative currents would have little or no effect on the distribution of charge at the specified sites when hyperpolarizing, but would reduce the rate of charge accumulation when given in conjunction with a positive current.

One should note that the physical model proposed above is not completely at variance with the currently accepted model for the nerve impulse in which conductance variables are entirely a function of membrane potential (Hodgkin and Huxley, 1952). (Indeed, for times short compared with the membrane time constant [and therefore normally too short to account for low-frequency repetitive firing], the Hodgkin-Huxley theory is sufficient to account for an apparent constant charge threshold in the case of a square wave current applied to a resting axon at a single point [Nobel, 1966; see p. 19–20].) It is simply suggested that in the *subthreshold domain* events which lead to spike initiation during repetitive activity may have a physical basis in the interaction between a charged internal species and specific sites on the membrane, and that this phenomenon may be described as a relaxation oscillator with a charging capacitance.

It must be emphasized that this model has been proposed to account for spike initiation in tonic neurons only, that is, in neurons which are capable of producing infinite trains of impulses at relatively low frequencies, and which show a *linear current-frequency relation*. It is precisely for such neurons that the voltage-determined model is inadequate to account for

repetitive spike initiation. Although it is clear that Hodgkin-Huxley model neurons are capable of responding to a constant depolarizing current with repetitive firing (Fitzhugh, 1961), the firing rate is proportional not to current, but to the logarithm of the current (Agin, 1964). Moreover, where additional voltage-dependent conductance changes with long time constants have been invoked and can apparently account for subthreshold pacemaker potentials (Nobel, 1962; Nobel and Tsien, 1968), these processes have (at least in one case) also resulted in a gross change in the general form of the action potential (Nobel, 1962).

The behavior of the impulse-generating model given by equation 10 plus condition *d* is given in the Results section and is shown to mimic the behavior of the crayfish stretch receptor neuron. Although it is possible to obtain analytic solutions for Δt in special cases (see Appendix), these generally require the solution of transcendental equations of the form

$$\mathfrak{C} = x + e^{-x},$$

where $\mathfrak{C}$ is a constant which depends on initial conditions at the start of each integration. It was felt that the simplest and least expensive procedure (in terms of computer time) was to utilize the digital simulation outlined above in order to calculate Δt.

Values of the constants τ, b', and A, and initial values of the variables of the variables G and J were specified at the beginning of each run. G was either held constant or followed a specified function of time. Output was a list of successive interspike interval times and the corresponding instantaneous frequencies.

Comparison of Analogue and Digital Models

The digital program differs from the analogue program in that it accomplishes the transformation of a continuous[1] function $S(t)$ into a train of impulses. The digital computer integral model summarized by equation 10, and first developed in a somewhat different form by Stevens (1964), serves as the basis for this transformation. It is basically a more detailed model than the analogue model (which is based on equation 1), since it specifies a definite procedure by which to generate impulses.

The relationship between the models can be seen by examining equation 10 and G and J vary slowly compared with Δt. Then we may write

$$A \approx (\overline{G - J})\ \Delta t = \frac{(\overline{G - J})}{f}, \qquad (11\,a)$$

where $\overline{(G\text{-}J)}$ is the average value of S in the interspike interval, and Δt ($= 1/f$) is the time between impulses. Comparison with equation 1 shows immediately that

$$A = 1/k. \qquad (11\,b)$$

Under appropriate conditions, the integral model has the property that the instantaneous frequency is proportional to the average value of the stimulus during the interspike interval. In particular, the behavior of the digital model can be described by equation 1, *provided that G and J are slowly varying functions.*

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[1] Actually, $S(t)$ is *continuous* only in an average sense (over times long compared with Δt), since it is decremented by a fixed amount at the time of each spike. Note, however, that it is truly continuous over the interval of integration.

This last condition was met in the current work in which simulation of the response of the tonic stretch receptor neuron was attempted. The analogue program was useful in examining the response of the model to simple excitatory input functions over a rather wide range of parameter settings, whereas the digital program was used to obtain detailed information of interspike intervals beginning from a rather narrow range of fixed initial conditions and parameter values.

Experiments

The preparation and experimental procedures were generally as described in Sokolove and Cooke (1971). Stretch receptor organs from the abdomen of crayfish (*Orconectes* sp.) were mounted in an experimental chamber and the receptor muscle fibers crushed with fine forceps. The sensory neuron of the tonic stretch receptor was impaled with two 3 M KCl-filled microelectrodes, one for passing current and the other for recording potentials, and a suction electrode was applied to the sensory axon for antidromic stimulation.

Impulses recorded with the intracellular microelectrode were amplified and used to trigger a circuit (for details see Sokolove, 1969) which produced an output voltage that was reset by each spike and decayed along a $1/t$ curve during the interval between successive spikes. The output of this "$1/t$ generator" was then amplified and displayed on a penwriter chart along with the output from the excitatory current monitor (Fig. 1 B). The points of least excursion of the $1/t$ trace above base line (just before resetting) thus provided a measure of the instantaneous frequency, and a smooth curve drawn through these points was equivalent to the continuous function $f(t)$, giving the number of impulses per unit time.

Both square steps and exponentially increasing "steps" of current were delivered to the preparation at various current intensities and lasted a minimum of 15 sec. The circuit for injecting exponential steps of current is shown in Fig. 1 A, and an example of penwriter display is seen in Fig. 1 B. The time constant of the exponential step was found by plotting the current-monitor output (Fig. 1 B, lower trace) on semilog paper. The responses of each neuron to various intensities of square and exponential current were compared with corresponding curves drawn by the analogue computer.

In experiments designed to examine PTD the stretch receptor organ was stretched until the slowly adapting neuron fired at a steady, moderate rate (5–15 sec^{-1}). Rapid trains of antidromic impulses were then produced by stimulating through the suction electrode at a rate of 100/sec for durations up to 1.8 sec. Impulses recorded with the intracellular microelectrode were displayed on an oscilloscope without time base movement and photographed on 35 mm film moving at 50 mm/sec. Intervals from the last spike in a train to the next "spontaneous" impulse (posttrain intervals) were measured from the film and plotted against the number of spikes in the train. Curves so obtained showed a characteristic shape (Sokolove and Cooke, 1971; also see Fig. 7), with posttrain intervals always being longer than pretrain intervals.

Parameter Estimation for Computer Models through Analysis of Experimental Curves

As indicated in previous sections, three parameters are needed to specify the current-determined after-inhibition model for either analogue or digital computer simulations:

b' = the inhibitory current increment per impulse,
τ = the time constant for decay of inhibition, and
k = the proportionality constant between frequency and current (or its reciprocal, the threshold A).

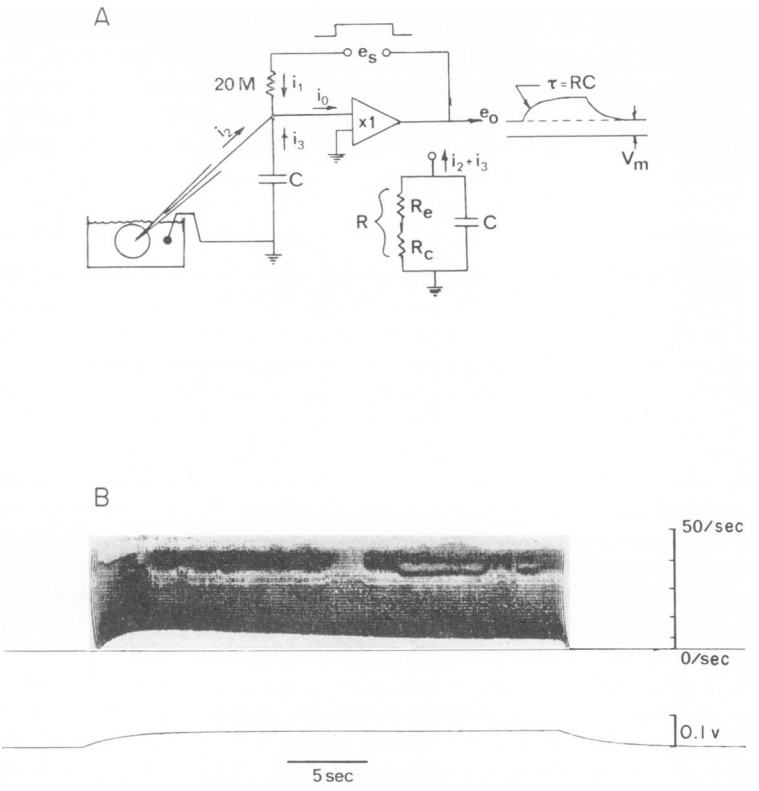

FIGURE 1 (A) Circuit used for applying exponential steps of current to a stretch receptor neuron. The unity gain amplifier used was a Picometric (Instrumentation Laboratory, Inc., Lexington, Mass.) with an input impedance greater than 10^{10} ohms and having a capacity neutralization circuit. e_s is the applied voltage; R_e and R_c are resistances of the microelectrode and cell respectively; C is the capacitor determining the time constant of the exponential step (with the electrode capacity compensated and the cell capacity negligible); V_m is the resting membrane potential. The following equations describe the circuit:

(*a*) $i_0 = i_1 + i_2 + i_3$,

(*b*) $i_0 = 0$,

(*c*) $e_0(t) = -i_2(t)R + V_m$,

(*d*) $i_1 = e_s/20 \times 10^{-6}$ amp.

Equations *a*, *b*, and *d* imply that the maximum current flowing through $R(i_{2_{max}})$ will be equal to $e_s/20$ μamp. Equation *c* implies that the time constant of the step can be determined from the output signal. (B) Upper trace: output of a $1/t$ generator triggered by impulses recorded with a second intracellular microelectrode (not shown in A). Bottom point of each vertical pen deflection is proportional to the instantaneous frequency. Lower trace: output of the unity gain amplifier in the current-injecting circuit (e_0). Voltage vs. time was plotted on semilog paper to give the time constant of the current step.

These parameters were estimated directly from experiments performed on the slowly adapting crayfish stretch receptor neuron and were then used in the computer programs.

The crayfish tonic stretch receptor neuron responds to a step of depolarizing current (G) with an initial high rate of firing (f_0) which then declines exponentially to a steady-state

frequency (f_∞) and continues at this frequency as long as the current is applied (Sokolove and Cooke, 1971). Both f_0 and f_∞ are proportional to current over a moderate range of intensities (usually 1.0–6.0 namp; see Fig. 2).

A series of step-depolarizing currents of different intensities was applied to a preparation and the corresponding curves of frequency decay were obtained. A semilog plot of frequency vs. time gave the time constant of the frequency decay τ_f at each value of current intensity, and the ratio f_0/f_∞ gave $1 + bk$ (equation 7). The time constant for decay of inhibition τ was then calculated directly from equation 8.

For each value of depolarizing current f_0 was plotted against G; the linear portion of each curve was fitted by a straight line (Fig. 2). The slope of this line gave k (equation 5 b), allowing b' to be calculated for each value of current. The values of $1 + bk$, b', and τ calculated for one cell are given in Table II.

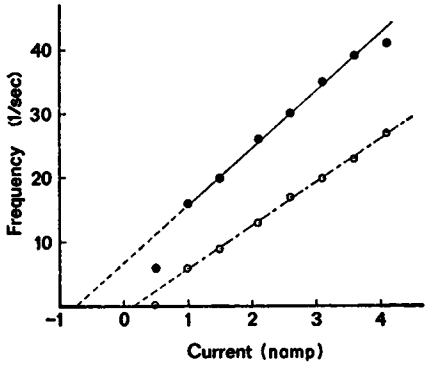

FIGURE 2 Initial (f_0, solid symbols) and steady-state (f_∞, open symbols) firing rates of a slowly adapting stretch receptor neuron subjected to different amounts of constant depolarizing current (G). Lines are drawn by eye. Note that the line drawn through the initial frequency points (f_0 vs. G) does not pass through the origin.

TABLE II

PARAMETERS OBTAINED IN ONE CELL FOR STEP CONSTANT CURRENTS COMPARED WITH SIMILAR PARAMETERS FROM A FIT OF THE DATA BY THE ANALOGUE MODEL

G	G^*(*)	f_0‡	f_∞	τ_f	$1 + bk$	b'		τ	
						Calc.	Model	Calc.	Model
namp	*namp*	*sec*$^{-1}$	*sec*$^{-1}$	*sec*		*namp*	*namp*	*sec*	*sec*
1.0	1.7	16	6	2.3	2.67	2.9×10^{-2}	3.1×10^{-2}	6.15	6.45
1.5	2.2	20	9	3.0	2.22	2.0×10^{-2}	1.9×10^{-2}	6.68	6.65
2.1	2.8	26	13	3.4	2.00	1.6×10^{-2}	1.6×10^{-2}	6.80	6.78
2.6	3.3	30	17	3.8	1.77	1.3×10^{-2}	1.3×10^{-2}	6.71	6.89
3.1	3.8	35	20	4.1	1.75	1.1×10^{-2}	1.1×10^{-2}	7.19	7.03
3.7	4.4	39	23	4.3	1.70	1.1×10^{-2}	1.0×10^{-2}	7.31	7.14
4.1	4.8	41	27	4.7	1.52	0.8×10^{-2}	0.8×10^{-2}	7.15	7.27

* $G^* = G - \gamma$; $\gamma = -0.7$ namp.

‡ $k = 9.1$ namp^{-1} sec^{-1} from a plot of f_0 vs. G.

For the majority of cells examined the linear portion of the f_0 vs. G curve followed the relation

$$f_0 = k(G - \gamma),$$

where γ, the x-intercept, $\neq 0$. The reasons for this are not currently understood but may be due to nonlinear behavior of the system at very low current intensities. (This is further indicated by the cell in Fig. 2 in which a constant depolarizing current of 0.5 namp was not able to produce sustained repetitive firing.) In such cases a "corrected" current, $G^* = G - \gamma$, was used as the excitatory input current for the analogue computer program simulation when comparison with the experimental data was attempted (see Table II).

With the estimated values of k, τ, and b' incorporated into the analogue program, curves of the $f(t)$ drawn by the analogue computer were compared with the corresponding experimental data. Often a better match between the experimental and computer-drawn curves was obtained if b' and τ were adjusted slightly; however, the adjusted values were never found to deviate by more than 10% from those initially calculated (Table II). The third parameter, k, was not adjusted, since it was found that the quality of the fit was seldom improved and usually worsened by departures from the originally estimated value.

RESULTS

Behavior of the Model in Response to Steps of Current and after Rapid Spike Trains Superimposed on Steady Firing

In order to examine the general behavior of the after-inhibition model, arbitrary values for the parameters k, τ, and b' were chosen for use in the computer simulations. The results of one experiment with k = 8.0 imp/namp-sec, τ = 10.0 sec,

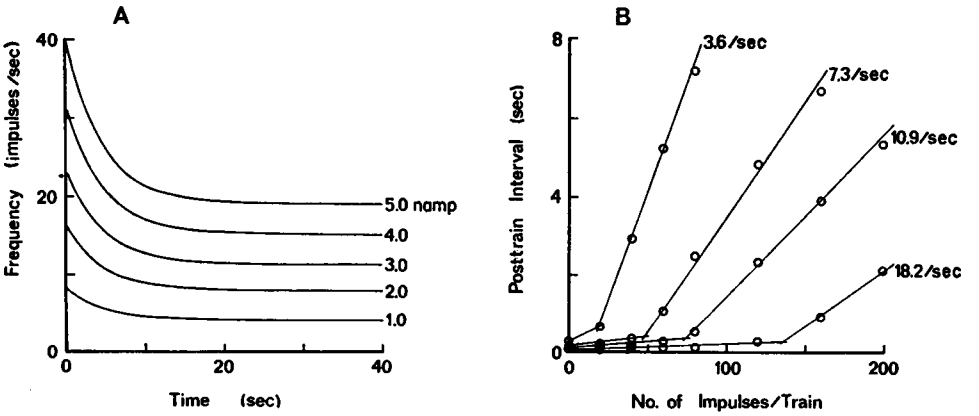

FIGURE 3 (A) Analogue computer simulation of adaptation to various intensities of suddenly imposed depolarizing currents. (B) Digital computer simulation of PTD caused by rapid trains of impulses superimposed on steady background firing. The duration of the interval from the end of the train to the first spontaneous spike is plotted against the number of spikes in the train. Lines shown are drawn by eye in order to indicate trends in the data. Background rates are given to the right of each curve.

and $b' = 0.015$ namp/imp were qualitatively similar to results obtained with other values and are shown in Fig. 3.

"Adaptation" to square steps of depolarizing current is shown by the analogue computer-drawn curves of Fig. 3 A. At each current value the frequency declined exponentially with a time constant $\tau_f = 4.75$ sec to a constant frequency f_∞ which was proportional to the current intensity. The buildup of inhibitory current was also exponential with the same time constant, and the steady-state value J_∞ was proportional to current intensity.

Next, the firing pattern after rapid trains of impulses superimposed on steady firing was simulated on the digital computer. The steady rates chosen were the values of f_∞ from the analogue simulation, since the corresponding values of G and J_∞ were already known. The total inhibitory current used as input for the digital program was $J_\infty + nb'$ where nb' represents the additional inhibition from a rapid train of n impulses. Posttrain interspike intervals computed for rapid trains containing 20–200 impulses are plotted against train length in Fig. 3 B.

Below a certain number of impulses per train only small increases are seen in the posttrain interspike interval; above this "threshold" number of impulses, the increases are much larger and are approximately linear with train length. Furthermore, the threshold is higher when the steady background frequency is greater.

A similar "threshold effect" in the crayfish tonic stretch receptor was extensively described by Sokolove and Cooke (1971). In their report it was pointed out that an apparent ambiguity existed: whereas the inhibitory effect of a train of impulses was assumed to increase linearly with the number of impulses per train, when duration of posttrain interval was plotted against train length there was an apparent discontinuity at a particular number of impulses per train (called the threshold number). Moreover, the threshold increased with an increase in the background firing rate. The fact that the after-inhibition model exhibits this type of threshold effect phenomenon strongly suggests that this model can closely simulate the behavior of a real crayfish stretch receptor neuron. The reasons which lead to the appearance of the threshold effect in the model will be considered in greater detail in the Discussion.

Comparison of Computed Curves and Experimental Curves Showing Response to Square and Exponential Steps of Current

Solid symbols in Fig. 4 show the response of one tonic stretch receptor neuron to various intensities of a suddenly applied depolarizing current (square steps). A plot of f_0 vs. G for this cell yielded a line with slope $k = 9.1$ imp/namp-sec and an x intercept $\gamma = -0.7$ namp. (Complete data for this cell are given in Table II.) Using the methods outlined above to estimate the remaining parameters the analogue computer was programmed to generate $f(t)$ curves in response to equivalent square steps of current (Fig. 4, solid lines). The values of current intensity shown

on the right of each curve in Fig. 4 are the corrected values for depolarizing current (G^*) given in Table II.

For small to moderate current intensities the computed curves agreed with the experimental ones; at higher intensities the experimental curve often showed a slightly more rapid initial decay for the first 2–3 sec. Attempts to match this initial portion by adjusting b' and τ in the analogue program resulted in a mismatch for the steady-state (flat) portion of the curve. The reasons for this discrepancy are not understood; however, it may be that sudden, *intense* depolarizing currents directly affect spike-generating mechanisms to produce an inhibitory effect which adds to the type of inhibition considered in this paper.

Stimulation was also effected through depolarizing currents, which rose in an

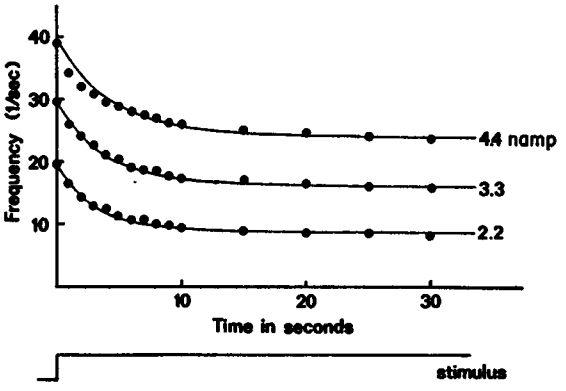

FIGURE 4 Adaptation of a slowly adapting stretch receptor neuron to constant depolarizing currents. Filled symbols are data from experiments on one neuron. Lines were drawn by an analogue computer programmed to simulate the frequency response of this neuron. Further explanation in text.

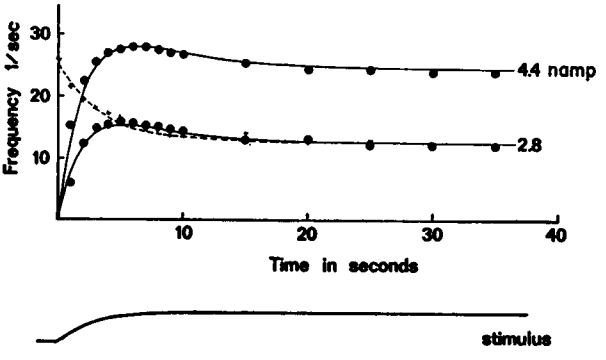

FIGURE 5 Frequency response of a slowly adapting stretch receptor neuron (solid symbols) and an analogue computer model (solid lines) to exponential current step. Time constant of steps is 2.5 sec. The broken line shows the response of the model to a square step of 2.8 namp (same cell as Fig. 4).

exponential manner to various constant levels (exponential steps). The response of the same cell as in Fig. 4 to exponential steps having a time constant of 2.5 sec is shown by the solid symbols in Fig. 5. Using the parameters previously obtained from the responses to square steps (Fig. 5, dashed line, shows one example), the analogue computer generated responses to equivalent exponential steps (Fig. 5, solid lines). The computed curves match the experimental ones very well, both with respect to rising and falling phases and with respect to maximum and steady-state values of the frequency. Similar results are shown in Fig. 6 for experiments in another cell in which exponential steps of faster time constant (0.4 sec) were employed.

Digital Computer Simulation of Posttrain Depression

As a further test of the validity of the model the digital computer simulation was used to predict the duration of interspike intervals after rapid trains of impulses superimposed on a background of steady firing. A stretch receptor preparation was stretched sufficiently to maintain a constant adapted firing rate of 5.5 imp/sec; after

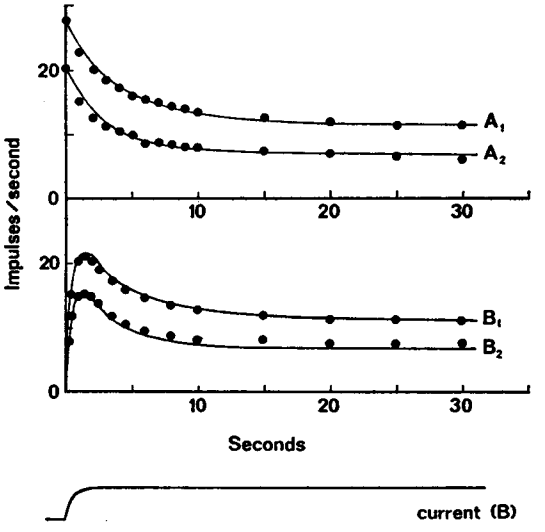

FIGURE 6

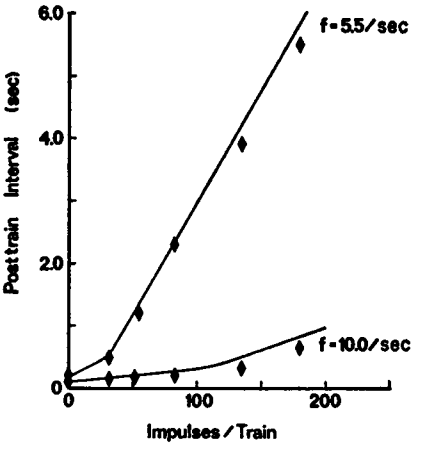

FIGURE 7

FIGURE 6 Frequency response of a slowly adapting neuron (solid symbols) and an analogue computer model (solid lines) to square and exponential current steps. Analogue program parameters were estimated from data obtained with square steps (A_1, A_2). Responses to the exponential step (B) were then predicted using the same parameters (B_1, B_2). Time constant of the exponential step was 0.4 sec. Current intensities were 4.1 namp in A_1, B_1, and 3.2 namp in A_2, B_2.

FIGURE 7 Simulation of posttrain depression. Filled symbols represent the intervals after antidromic trains in a slowly adapting stretch receptor neuron firing steadily because of moderate stretching. Different degrees of stretch produced steady rates of 5.5 and 10.0 imp/sec. Lines were drawn through sets of points taken from a digital computer simulation of the after-inhibition model under similar conditions. See text for details.

TABLE III

VARIATION OF CERTAIN PARAMETERS WITH INTENSITY OF CONSTANT CURRENT STEPS IN FIVE CELLS

Cell	k	G	$1 + bk$	τ	b'
	namp^{-1} *sec*$^{-1}$	*namp*		*sec*	*namp*
A	9.1	1.0	2.82	6.5	0.031
		1.5	2.18	6.7	0.019
		2.1	2.00	6.8	0.016
		2.6	1.81	6.9	0.013
		3.1	1.73	7.0	0.011
		3.7	1.64	7.1	0.010
		4.1	1.55	7.3	0.008
(Mean ±SEM)			1.96 ±0.40	6.9 ±0.6	0.015 ±0.007
B	6.5	3.2	2.80	12.9	0.022
		4.2	2.43	11.1	0.020
		5.1	1.89	10.0	0.014
		6.2	1.74	8.9	0.012
			2.21 ±0.42	10.7 ±1.5	0.017 ±0.004
C	6.4	2.5	6.38	9.6	0.088
		3.2	3.24	8.3	0.042
		4.2	2.28	8.7	0.023
		5.2	1.90	6.9	0.021
		6.3	2.08	9.7	0.018
			3.18 ±1.66	8.6 ±1.0	0.038 ±0.026
D	8.5	1.0	3.29	16.5	0.016
		2.0	2.10	9.0	0.014
		3.0	2.10	13.2	0.010
		4.0	1.77	12.5	0.007
		5.0	1.68	10.7	0.007
			2.19 ±0.58	12.4 ±2.5	0.011 ±0.004
E	9.5	2.5	2.52	5.5	0.029
		3.1	2.04	5.0	0.022
		3.6	1.95	5.6	0.018
		4.2	1.67	6.0	0.012
			2.05 ±0.31	5.5 ±0.4	0.020 ±0.006

some time it was stretched further, to fire at 10.0 imp/sec. At each steady frequency the cell was subjected to antidromic trains of 30–180 impulses, at a rate of 100/sec. Posttrain intervals were recorded and plotted as a function of the number of impulses per train (in Fig. 7, solid symbols).

Stretch was then released and current steps of moderate intensity levels were applied to the resting cell. From the degree and time-course of frequency adaptation to these constant currents the parameters required by the digital computer program were estimated. Two sets of posttrain intervals were calculated by the digital com-

puter program after trains of 20–200 impulses. These two sets corresponded to steady background firing levels of 5.5 and 10.0 imp/sec. The solid lines in Fig. 7 are smooth curves drawn through the two sets of points.

Again, simulation results agree well with the experimental data. Even the threshold effect is reproduced at about the correct number of impulses for each "spontaneous" firing rate. Differences between the calculated and observed posttrain intervals are seen to increase for trains containing more than 100 impulses, and are probably the result of errors in estimating either τ or b' for this cell (see next section).

Variation of Parameters with Intensity of Depolarizing Current

A summary of the data from experiments on five tonic stretch receptor cells is given in Table III (the complete data for cell A were given previously in Table II). In a given cell different values of τ, $1 + bk$, and b' were usually found at different current intensities. In general τ increased somewhat with increasing current. More striking, however, was the decrease in b', and therefore in $1 + bk$ ($b = b'\tau$), which occurred with increasing intensity of depolarizing current.

This result is not predicted by the after-inhibition model, and in fact contradicts an implied assumption of the theory: that the parameters k, τ, and b' are constant for a given tonic nerve cell. The systematic variation in b' implies that the inhibitory current per impulse decreases with depolarization, and suggests that it may increase with hyperpolarization (see Discussion).

Magnitude and Decay Constant of PTH Predicted and Observed

It is known that DC adaptation and PTD in the tonic stretch receptor result from the operation of an electrogenic sodium pump (Sokolove and Cooke, 1971), and that this pump also produces a PTH after a train of impulses in the resting cell (Nakajima and Takahashi, 1966; Sokolove and Cooke, 1971). If the current-determined after-inhibition model has physical significance, then one should be able to predict the size and decay constant of PTH using parameters obtained from adaptation data.

Fig. 8 A shows the frequency response of one cell (Table III, cell E) to constant depolarizing currents of 2.5–4.2 namp. The average values of τ, the decay constant of the inhibitory process, and of b', the inhibitory current per impulse, were 5.5 ± 0.4 sec and 0.020 ± 0.006 namp/imp, respectively. In addition, the total cell resistance R_c was measured with short hyperpolarizing current pulses and found to be 4.0 MΩ. If each impulse results in an inhibitory (hyperpolarizing) current of b' namp and this flows across the total membrane resistance, then after a rapid train of 100 antidromic impulses in the cell there should be a PTH of $(100)(b')(R_c)$ mv which decays with a time constant of τ sec. The calculated values of PTH and τ are compared in Table IV with those actually observed after a 1 sec train of 100 antidromic impulses in this cell (illustrated in Fig. 8 B).

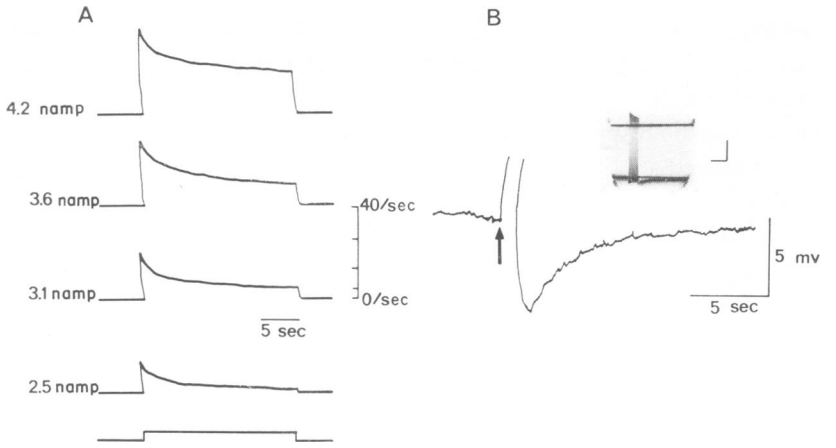

FIGURE 8 PTH predicted from adaptation data. (A) Tracings of instantaneous frequency records for the response of one cell to various intensities of depolarizing current. (B) Penwriter records of PTH after an antidromic train of 100 impulses in the same cell. Train begins at arrow; impulses are off scale. The inset shows an oscilloscope record at lower gain of a similar experiment. It can be seen that spike height is decreased by about 10% during the rapid train. Inset calibration: vertical = 25 mv, horizontal = 2 sec. From the adaptation curves in A the size and decay constant of PTH were calculated. These were found to be comparable to the values measured from records like that in B (see Table IV).

TABLE IV

POSTTETANIC HYPERPOLARIZATION: PREDICTED FROM ADAPTATION DATA AND OBSERVED IN A STRETCH RECEPTOR NEURON

	PTH	τ_{PTH}
	mV	*sec*
Calculated	8.0 ±2.4	5.5 ±0.4
Observed (5 trials)	6.0 ±0.4	4.8 ±0.5

The agreement is satisfactory, although the observed averaged values of both the initial size of PTH and the decay constant are somewhat lower than the calculated ones. Reasons for this result will be considered in the Discussion.

DISCUSSION

Limits on the Model

The results presented here indicate that the after-inhibition model can simulate the behavior of the slowly adapting stretch receptor neuron to at least a first-order approximation: (*a*) both the model and the biological system "adapt" similarly in response to a constant depolarizing current; (*b*) both the model and the neuron show depressed activity after a high-frequency train of impulses, with a so-called

threshold effect related to the number of impulses in the train; (*c*) finally, by calculating three parameters from adaptation data of any one neuron, and incorporating these parameters into the model, it is possible to mimic the behavior of that neuron with respect to square and exponential steps of depolarizing current, and to predict the size of PTH in that neuron (if the total cell resistance is known).

It should be emphasized, however, that the above statements apply only over a limited range of conditions. For example, the present investigations have been confined to a range within which equation 1 was found to hold true. Thus, no attempt was made to apply the model when (*a*) the magnitude of a depolarizing current was too small to sustain repetitive firing, or (*b*) the current was large enough to produce an initial rate of firing larger than about 45/sec. Even within these constraints it was found that at least one parameter (b') was not constant as assumed, but varied with the applied current.

Here I first discuss the threshold effect and examine the significance of certain parameters in the after-inhibition model. Then I consider inconsistencies between the simple after-inhibition model and the tonic stretch receptor neuron.

The Threshold Effect in Simulation of PTD

As described earlier, the digital computer program used to simulate PTD used an integration rule to determine the times of spike production (equation 10). In this algorithm the continuous current $S(t)$ is integrated until some limit A is reached, whereupon a spike time is recorded and the integral is reset to zero. The integral, however, is constrained to be nonnegative; it is held at zero until such time as the integrand begins to take on positive values. It is this feature of the digital program which leads to the appearance of a threshold effect when PTD is simulated. The following example illustrates this point.

Let us construct a cell with the following parameters:

k = 8.0 imp/namp-sec,
τ = 10.0 sec, and
b' = 0.015 namp/imp.

Then the application of a constant depolarizing current G of 2.0 namp will eventually lead to a steady state in which f_∞ = 7.3 imp/sec and J_∞ = 1.08 namp. If we now superimpose a rapid train of n impulses, this will add $J_+ = nb'$ namp to the steady-state inhibition (J_∞) already accumulated. The values of total posttrain inhibitory current ($J_\infty + J_+$), and of the corresponding posttrain intervals are tabulated in Table V for trains containing 20–100 impulses.

It can be seen that as total inhibitory current *exceeds* the excitatory current, posttrain intervals become many seconds long rather than hundreds of milliseconds long. This occurs because, after a sufficiently long train, S is negative and the in-

TABLE V

THE THRESHOLD EFFECT IN A MODEL CELL

No. of impulses per train	J_+	$J_\infty + J_+$	Posttrain interval
	namp	*namp*	*sec*
—	—	1.08	0.137
20	0.30	1.38	0.201
40	0.60	1.68	0.368
60	0.90	1.98	1.09
80	1.20	2.28	2.50
100	1.50	2.58	3.63

G = 2.0 namp, f_∞ = 7.3 imp/sec, J_∞ = 1.08 namp.

tegral is zero. Moreover, it *remains zero* until S turns positive (because of decay of J), whereupon integration begins and continues until the limit A is reached. After shorter trains, S is still reduced by the added inhibitory current, but as long as it is positive, integration will begin immediately after the train ceases. Thus, the threshold effect occurs when the number of impulses in a train causes the inhibitory current to exceed the excitatory current. Above threshold, long delays result from the negative value of S (and consequent zero value of the integral) for some time after a train.

The intracellular counterpart to the threshold phenomenon is possible to predict qualitatively, but difficult to observe experimentally. Presumably, all suprathreshold (long) trains result in an inhibitory current larger than the excitatory one and should therefore cause a hyperpolarization below the level of the original resting potential leading to a much prolonged posttrain interval. (Subthreshold [short] trains ought only to produce a reduced rate of rise of the prespike potential.) When steady firing was faster than about 6 imp-sec^{-1}, a posttrain hyperpolarization below the resting potential was never observed during any suprathreshold posttrain interval. At steady rates lower than 6 sec^{-1} the expected hyperpolarization could not be distinguished from the normal spike afterpotential, except in very slowly firing cells when very long trains were employed (Sokolove and Cooke, 1971). Perhaps the negative result can be partially accounted for by the fact that the recording electrode in the soma was somewhat removed from the spike-initiating zone. Thus, even if an inhibitory current were sufficient to produce hyperpolarization in that zone, it might have failed to do so at the recording site.

Significance of Certain Parameters in the Current-Determined After-Inhibition Model

The use of a current-determined rather than a voltage-determined model of after-inhibition yields certain parameters which may be of physical significance when applied to real nerve cells. For example, it has already been shown that b', the inhibitory current per impulse, can be used to predict the size of PTH in a resting cell.

Thus it probably represents the increase in electrogenic Na pump current caused by the influx of Na^+ during a single impulse.

The inhibitory decay constant τ should be equivalent to the decay constant for PTH, and thus probably reflects the rate at which Na^+ is removed from the cell. If one assumes the rate of Na pumping to be proportional to the internal Na concentration (Brinley and Mullins, 1968) so that

$$\frac{d[Na]_i}{dt} = -\alpha[Na]_i ,$$

then one can easily show that the pumping rate constant α equals τ^{-1} (Sokolove, 1969). Thus, another of the model parameters is of significance with respect to the underlying physical process.

Also of interest is the integral threshold A (equation 10), which is a parameter having units of charge per impulse. Equation 10 shows that A represents *the charge which must accumulate to fire an impulse*. Nothing is said here of a depolarizing *voltage* threshold for impulse initiation. In the current-determined model variations in the depolarizing threshold may occur (see Eyzaguirre and Kuffler, 1955, p. 102, for an example of the shift in threshold with increasing frequency in the slowly adapting stretch receptor neuron), but the charge per impulse necessary for spike generation remains constant. This constraint leads directly to a linear current-frequency relation as indicated by equation 11 *a*. Equation 10 might reasonably be applied to neurons (or axons) capable of a maintained discharge, since most of these do show a linear current-frequency relation. It is therefore possible that the current-determined model for spike initiation may lead to a deeper understanding of the physical processes responsible for slow, sustained, repetitive firing.

Size and Time Constant of PTH: Expected and Observed

Although the calculated and observed values for size and decay constant of PTH in a single cell are reasonably close, both of the observed values are somewhat lower than the calculated ones. A high value for τ calculated may be partly explained by the observation that depolarizing currents normally cause an increase in the decay constant of PTH (Sokolove, 1969). Thus, the decay constant of PTH in the resting cell will tend to be faster than the inhibitory decay constant calculated from adaptation to constant depolarizing currents.

The larger size of the calculated PTH may be due to an overestimate of b'. It has been seen in Table III that b' decreased as the current, and therefore the average firing rate, increased. The high-frequency train preceding PTH might thus have contained less inhibitory current per impulse than the average value calculated from the adaptation data. From a more physical point of view this suggests that less Na^+ entered during the 100/sec train than expected, and therefore PTH was smaller than calculated. Evidence supporting this view is that spike height often decreased signifi-

cantly (~10%) during the rapid train preceding PTH (see inset, Fig. 8 B). Also, the duration of the train (1 sec) was long enough to allow significant decay of the hyperpolarization contributed by the first 20 or so spikes in the train.

Finally, it must be noted that spikes were initiated by antidromic stimulation of the sensory nerve which contains the axon of the tonic stretch receptor cell; however, this nerve also contains an axon which when stimulated inhibits stretch receptor discharge by lowering the membrane resistance of the sensory cell. Although care was taken at the beginning of each experiment to stimulate below the threshold for the inhibitor axon, the possibility remains that this threshold shifted during the course of the experiment. If both the sensory axon and the inhibitor axon were being stimulated simultaneously, then the reduced membrane resistance would result in a lower spike height and smaller PTH than expected, and perhaps a smaller τ.

Experimental Observations Not Accounted for by the Model

As mentioned previously, in the crayfish slowly adapting stretch receptor neuron the quantity b' was found to vary inversely with the intensity of applied depolarizing current, rather than remaining a fixed parameter. Since the inhibitory current per impulse appeared to decrease with increasing depolarization, it might therefore be expected to increase with hyperpolarization; however, if inhibitory current is equivalent to the hyperpolarizing electrogenic Na pump current found in this sensory neuron, then PTH should also decrease with depolarization and increase with hyperpolarization. Evidence in partial support of this prediction has been found by Nakajima and Takahashi (1966), who observed that hyperpolarization did, indeed, increase the size of PTH. Finally, compatible evidence has been reported which indicates that membrane potential directly affects the rate constant of the Na pump in this cell: depolarization slows the pump, while hyperpolarization speeds it up (Sokolove, 1969).

This last observation might also help to explain another inconsistency between a prediction of the model and one experimental result in the stretch receptor cell. A convenient test of the simple after-inhibition model first suggested by Stevens (1964) is to use hyperpolarizing pulses to stop ongoing firing and hence allow inhibition to decay. After the release of hyperpolarization a transient increase in the firing rate should be seen because of the decreased inhibition. According to the model, the size of this "rebound" transient should be independent of the magnitude of the imposed hyperpolarizing pulse (Stevens, 1964; Purple and Dodge, 1966); however, in the tonic stretch receptor neuron I observed that the rebound was *not* independent of the pulse magnitude and was, in fact, proportional to the intensity of the imposed current. This may have been because of the effect of the hyperpolarizing pulse on the electrogenic Na pump, but substantiation of this view will require new experimental data showing the relationship between membrane potential and size and time-course of PTH.

Applicability of the After-Inhibition Model

In the case of the stretch receptor cell it was already known that the process responsible for after-inhibition involved an electrogenic Na pump and the relevant predictions could be experimentally verified. In other systems, however, an inhibitory process may be suspected but not yet identified. For example, the cat muscle spindle receptor has been shown to adapt to depolarizing currents (Emonét-Denand and Houk, 1969), but the adaptation mechanism has not yet been determined. The after-inhibition model might be used in this case to ascertain the magnitude and time-course of the underlying process.

This paper is based on part of the doctoral dissertation of Dr. Sokolove which was submitted to the Committee on Higher Degrees in Biophysics, Harvard University, May 1969, in partial fulfillment of the requirements for the Ph.D. degree.
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APPENDIX

The problem is, given a set of initial conditions, to calculate the duration of an interspike interval (T) for a system which behaves according to equation 10 with the constraint that the integral in that equation must be either positive or zero. Two sets of initial conditions will be considered for the case of a constant excitatory current G: (*a*) $J_0 \geq G$ and (*b*) $J_0 < G$ where $J_0 = J(t = 0)$ and $J(t) = J_0 e^{-\lambda t}$. (Note: $\lambda = 1/\tau$.)

$$A = \int_0^T S \, dt = \int_0^T G - J \, dt. \tag{10}$$

Case I: $J_0 \geq G, S = G - J_0{}^{-\lambda t}$

Let t_0 be the time at which S becomes zero because of decay of J.

$$S(t_0) = 0 \Rightarrow G = J_0 e^{-\lambda t_0}.$$

Thus

$$t_0 = (1/\lambda) \ln (J_0/G). \tag{A 1}$$

For all $0 \leq t \leq t_0$, the integral in equation 10 is zero; equation 10 thus becomes

$$A = \int_{t_0}^T S(t) \, dt = \int_{t_0}^T [G - J_0 e^{-\lambda t}] \, dt. \tag{A 2}$$

Evaluating equation A 2 and letting $x = \lambda(T - t_0)$ so that

$$T = (x/\lambda) + t_0, \tag{A 3}$$

gives

$$(A\lambda/G) + 1 = x + e^{-x}. \tag{A 4}$$

Equation A 4 is transcendental and therefore cannot be solved analytically; however, a solution for x can be obtained either by graphically evaluating the function $g(x) = x + e^{-x}$ or by applying various root-searching procedures with the aid of a computer. Once x is found, T can be evaluated from equations A 3 and A 1:

$$T = (1/\lambda)\,[x + \ln\,(J_0/G)]. \tag{A 5}$$

Case II: $J_0 < G$, $S = G - J_0e^{-\lambda t}$

In this case

$$t_0 = (1/\lambda)\,\ln\,(J_0/G) < 0. \tag{A 6}$$

Evaluating the integral in equation 10 over the interval 0-T now gives:

$$A = GT + (J_0/\lambda)(e^{-\lambda T} - 1). \tag{A 7}$$

Combining with equation A 6, rearranging terms, and letting $x = \lambda(T - t_0)$ as before, this becomes

$$[(A\lambda + J_0)/G - \ln\,(J_0/G)] = x + e^{-x}. \tag{A 8}$$

As in case I, x can be found using either graphical or root-searching techniques and T can then be calculated from equation A 5. (Note that when $J_0 = G$, equation A 8 is equivalent to equation A 4.) Although in both case I and case II final evaluation of T is made using equation A 5, important differences exist:

(*a*) In case I, x is *independent* of J_0 and $\ln(J_0/G)$ is positive;

(*b*) In case II, x is a function of J_0 as well as A, λ, and G, and $\ln(J_0/G)$ is negative.

These differences account for the threshold effect observed when a high-frequency train is superimposed on steady firing and the first posttrain interval (T) is plotted against the number of spikes in the train (PTD). When the number of spikes is small enough so that immediately after the train $J_0 < G$ (case II), T will increase with spike number because of the dependence of x on J_0. The rate of increase, however, will be reduced because of the logarithmic term. When the number of spikes becomes large enough so that $J_0 \geq G$ (case I), x is independent of J_0 and T should increase with spike number according to the relation

$$T = (1/\lambda)\,\ln\,(J_0/G) + \text{const.} \tag{A 9}$$

Unfortunately, the data collected in the stretch receptor study reported here were insufficient to make an adequate test of this prediction.

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