Contributions of Ion Conductances to the Onset Responses of Octopus Cells in the Ventral Cochlear Nucleus: Simulation Results

YIDAO CAI, JoANN McGEE, AND EDWARD J. WALSH
Developmental Auditory Physiology Laboratory, Boys Town National Research Hospital, Omaha, Nebraska 68131

Cai, Yidao, JoAnn McGee, and Edward J. Walsh. Contributions of ion conductances to the onset responses of octopus cells in the ventral cochlear nucleus: simulation results. J. Neurophysiol. 83: 301–314, 2000. The onset response pattern displayed by octopus cells has been attributed to intrinsic membrane properties, low membrane impedance, and/or synaptic inputs. Although the importance of a low membrane impedance generally is acknowledged as an essential component, views differ on the role that ion channels play in producing the onset response. In this study, we use a computer model to investigate the contributions of ion channels to the responses of octopus cells. Simulations using current ramps indicate that, during the “ramp-up” stage, the membrane depolarizes, activating a low-threshold K+ channel, $K_{\text{LT}}$, which increases membrane conductance and dynamically increases the current required to evoke an action potential. As a result, the model is sensitive to the rate that membrane potential changes when initiating an action potential. Results obtained when experimentally recorded spike trains of auditory-nerve fibers served as model inputs (simulating acoustic stimulation) demonstrate that a model with $K_{\text{LT}}$ conductance as the dominant conductance produces realistic onset response patterns. Systematically replacing the $K_{\text{LT}}$ conductance by a h-type conductance (which corresponds to a hyperpolarization-activated inward rectifier current, $I_h$) or by a leakage conductance reduces the model’s sensitivity to rate of change in membrane potential, and the model’s response to “acoustic stimulation” becomes more chopper-like. Increasing the h-type conductance while maintaining a large $K_{\text{LT}}$ conductance causes an increase in threshold to both current steps and acoustic stimulation but does not significantly affect the model’s sensitivity to rate of change in membrane potential and the onset response pattern under acoustic stimulation. These findings support the idea that $K_{\text{LT}}$, which is activated during depolarization, is the primary membrane conductance determining the response properties of octopus cells, and its dynamic role cannot be provided by a static membrane conductance. On the other hand, $I_h$, which is activated during hyperpolarization, does not play a large role in the basic onset response pattern but may regulate response threshold through its contribution to the membrane conductance.

INTRODUCTION

Octopus cells make up one of the unique cell types in the auditory system. They reside in a restricted area (the octopus cell area) in the posteroventral cochlear nucleus (PVCN) (Osen 1969). Their large cell bodies and large but sparsely branched dendrites are matched only by those of large multipolar stellate cells, also residing in the PVCN (Golding et al. 1995; Kane 1977; Smith and Rhode 1989). Physiologically, octopus cells usually respond at stimulus onset with a single action potential followed by a steady-state depolarization under current stimulation (Feng et al. 1994; Romand 1978) or with a major response peak early in the poststimulus histogram (PSTH) and little or no response during the steady-state under acoustic (tonal) stimulation in vivo (Godfrey et al. 1975; Rhode and Smith 1986; Rouiller and Ryugo 1984). Octopus cells have a very low membrane resistance, with membrane time constants as short as 200 $\mu$s (Golding et al. 1995, 1999). As a result, it is difficult to study these neurons intracellularly, and voltage-clamp data are not available. In response to acoustic stimuli, octopus cells show remarkable temporal precision in their spike activity relative to stimulus onset and therefore may play a role in the processing of pitch information in complex stimuli (Cai et al. 1998; Golding et al. 1995; Oertel 1991; Rhode 1995).

The unique response feature of octopus cells (i.e., the onset response pattern) has been attributed to intrinsic membrane properties, low membrane impedance, synaptic inputs, or combinations of these influences (Cai et al. 1997a; Evans 1998; Feng et al. 1994; Golding et al. 1995; Levy and Kipke 1997, 1998). In the most commonly held view, the low membrane impedance, coupled with a short membrane time constant, is emphasized in the production of onset responses, which require multiple subthreshold inputs that coincide temporally to produce a suprathreshold response (“coincidence detection”) (Evans 1998; Golding et al. 1995). In accordance with this view, a large leakage conductance has been used to represent the influence of certain identified ion conductances in one computational model (Levy and Kipke 1997), whereas other studies have emphasized factors like the effectiveness of synaptic inputs and dynamic spike thresholds as the principal determinants of onset responses (Kipke and Levy 1997; Levy and Kipke 1998).

Although the role of ion channels in the production of onset responses has been recognized (Cai et al. 1997a; Feng et al. 1994; Ferragamo and Oertel 1998; M. J. Ferragamo and D. Oertel, unpublished data; Golding et al. 1995), opinions regarding their exact contributions vary. Earlier studies emphasized the Na+ channel, suggesting that its inactivation prevents the initiation of further spiking events after the initial onset spike (“depolarization block”) (Feng et al. 1994; Ritz and Brownell 1982). However, results from a brain slice preparation suggest that action potentials are not initiated in the soma of octopus cells (Golding et al. 1995), and computer simul-
tions suggest that membrane depolarization does not necessarily lead to depolarization block when a low-threshold $K^+$ channel ($K_{LT}$) is present (Cai et al. 1997a). Recently, two primary types of ion channels/currents have been identified in octopus cells: a $K_{LT}$ channel that is sensitive to 4-aminopyridine (4-AP) and $\alpha$-dendrotoxin, and an inward rectifier current ($I_h$) that is activated during hyperpolarization and is sensitive to Cs$^+$ (the conductance corresponding to $I_h$ will be referred to as h-type conductance and denoted by $g_{I_h}$). Golding et al. (1995, 1999) demonstrated that blocking $I_h$ with Cs$^+$ sharply increases the membrane resistance and prolongs the membrane time constant 20-fold. On the other hand, using computer simulations, Cai et al. (1997a) demonstrated the importance of the $K_{LT}$ channel in the production and regulation of onset responses in octopus cells by “injecting” current into model cells (which include a large h-type conductance), confirming an earlier suggestion made by Feng et al. (1994). Recent current-clamp studies also support the role of $K_{LT}$ in the onset response of octopus cells. Ferragamo and Oertel (1998), Ferragamo and Oertel, unpublished data, observed a sharp increase in membrane resistance (20-fold) after blocking $K_{LT}$ with $\alpha$-dendrotoxin and 4-AP. Their data also revealed that action potential initiation in octopus cells depends on the rate that membrane potential changes after current injection (i.e., if the current is ramped, it may not produce an action potential even if it is suprathreshold when presented as a step).

Thus it seems that two basic questions must be addressed: one is whether active ion channels merely provide a low membrane impedance (i.e., whether a low membrane impedance is sufficient to produce the response features of octopus cells), and the other is what are the contributions of $K_{LT}$ and $I_h$ to the responses of octopus cells.

We address these questions using a computational model of the octopus cell that allows us to monitor ion conductance changes without interfering with the responses of the model cell and to simulate both in vitro intracellular responses and in vivo physiological responses using the same set of model parameters. In this study, we made the $K_{LT}$ conductance ($g_{K_{LT}}$) the dominant conductance in the model initially, then gradually replaced $K_{LT}$ conductance with h-type conductance or a leakage conductance while maintaining a constant overall resting membrane conductance or increased $g_{I_h}$ without changing $g_{K_{LT}}$. Through these manipulations we studied the contributions of $K_{LT}$ and $I_h$ as well as whether or not the conductance mainly provided by $K_{LT}$ channels might be replaced by a static (leakage) membrane conductance. Ramped currents were used to simulate the sensitivity of octopus cells to the rate of membrane potential change, and spike trains recorded from auditory-nerve fibers were used to simulate acoustic stimulation. The sensitivity of action potential initiation to rate of change in membrane potential (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data) and the onset PSTH pattern (Godfrey et al. 1975; Rhode and Smith 1986) served as main criteria to evaluate the performance of the model.

Our results further support the view that $K_{LT}$ plays an important role in the octopus cell responses and suggest that it is the most important factor affecting their temporal response properties. It not only contributes to the low membrane resistance, but more importantly, it dynamically adjusts its conductance in response to stimuli. Such dynamic changes in the $K_{LT}$ conductance (and thus the overall membrane conductance) are the basis for the dynamic changes in the effectiveness of synaptic inputs and spike threshold suggested by Levy and Kipke (1998). In addition, we showed that the h-type conductance is probably not an important determinant of the transient response of octopus cells. However, a large $I_h$ contributes to the low membrane resistance and may be involved in the regulation of sensitivity of the neuron in vivo.

**Methods**

**Model description**

The basic structure of the octopus cell model used in this study, which was based on available anatomical and physiological data (Golding et al. 1995; Kane 1973; Oertel et al. 1990; Rhode et al. 1983; Schwartz and Kane 1977), is the same as in previous studies (Cai et al. 1997a). However, in this study, the relative contribution of $K_{LT}$ conductance was increased and that of h-type conductance was decreased or $g_{I_h}$ was changed without changes to $g_{K_{LT}}$. In addition, the membrane resistivity ($R_m$) was increased. We briefly describe the model in the following text, emphasizing the changes incorporated for this study.

As schematized in Fig. 1A, the soma of the model neuron was 32 $\mu$m in diameter, its axon was 3 $\mu$m in diameter and 70 $\mu$m in length, and four identical dendrites were each 5 $\mu$m in diameter and 200 $\mu$m in length. Dendrites were modeled as cylinders for simplicity, even though the dendrites of octopus cells taper slightly (Golding et al. 1997, 1999) compared with the original estimate of $190 \mu$m (Golding et al. 1995; Kane 1973; Morst et al. 1973; Oertel et al. 1990; Ostapoff et al. 1994; Rhode et al. 1983; Schwartz and Kane 1977). The axon and the soma were each represented by a single compartment. Each of the four dendrites were divided into 20 sections of equal length and thus were represented by the same number of compartments (Fig. 1B).

The basic electrical parameters of the model were either standard values or were selected from standard ranges (Jack et al. 1983) and adjusted to fit available physiological data. Specifically, the membrane capacitance density ($C_m$) was set to 1 $\mu$F/cm$^2$, and the axial resistivity ($R_a$) to 100 $\Omega$cm, as typically reported in neuronal models (Jack et al. 1983). In accordance with the new data that octopus cells may have a membrane time constant as low as 200 $\mu$s (Golding et al. 1997, 1999) compared with the original estimate of ~1 ms (Golding et al. 1995), the passive membrane resistivity ($R_m$) was changed from the 1 k$\Omega$cm$^2$ in the original model to the present 2 k$\Omega$cm$^2$, resulting in a smaller leakage conductance or a higher resistance. However, the maximum conductance of the $K_{LT}$ channel was increased, making it the major factor contributing to the resting membrane conductance. As a result, the total resting membrane conductance was increased (resistance decreased) compared with the original model. The decision to increase the contribution of $g_{K_{LT}}$ was based mainly on the observation that although the original model was sensitive to the ramp time during the initiation of an action potential (Fig. 2A), the model was not as sensitive as neurons in vitro. Doubling the $K_{LT}$ conductance increased the model’s sensitivity to the ramp time (Fig. 2B). The use of a large $K_{LT}$ conductance was also consistent with previous simulation results (Cai et al. 1997a) and with recent experimental data (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data), both of which demonstrated that $K_{LT}$ plays a larger role in shaping the responses of octopus cells than earlier experimental data suggested (Golding et al. 1995). The basic electrical parameters, together with the morphological parameters, determine other passive electrical parameters used in the model. The resting membrane potential was set to $-62$ mV and was based on the range of values observed in intracellular recordings from octopus cells (Feng et al. 1994; Golding et al. 1995; Romand 1978; Rouiller and Ryugo 1984). As shown in Fig. 1C, each compartment contained a capacitor representing membrane capacitance ($C_m$) and a leakage branch consisting of a leakage conductance ($g_{leak}$) and a battery ($E_{leak}$). For...
passive compartments, the leakage equilibrium potential $E_{\text{leak}}$ equals the resting membrane potential. For compartments with ion channels, one of $g_{\text{leak}}$ and $E_{\text{leak}}$ is fixed, and the other is adjusted to maintain a stable resting membrane potential as in Rothman et al. (1993). As in the original model, the dendritic compartments are passive while the soma and axon compartments contained ion channels. For the axon compartment, $E_{\text{leak}}$ is fixed at $-53$ mV and $g_{\text{leak}}$ is adjusted to be $2.57$ nS. For the soma compartment, $g_{\text{leak}}$ is fixed at $16$ nS, and $E_{\text{leak}}$ is adjustable, having a value of $46$ mV for the basic parameter set.

The axon compartment contained exclusively Hodgkin-Huxley-type Na$^+$ and K$^+$ channels, which are responsible for generating action potentials. The soma compartment also contained these two channels, but their maximum conductances in the soma compartment are low, based on the suggestion that action potentials are generated at the axon hillock in octopus cells (Golding et al. 1995). Two other ion channels (currents) were included in the soma compartment: a low-threshold K$^+$ channel, $K_{\text{LT}}$, and a hyperpolarization-activated inward rectifier current, $I_{\text{h}}$, which are known to exist in octopus cells (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data; Golding et al. 1995). To maximize the dynamic role of the $K_{\text{LT}}$ channel, its kinetics were adjusted to a faster rate than in the original model (Cai et al. 1997a), the voltage-activation curve was steeper, and a smaller portion of channels are now open at rest ($g_{K_{\text{LTmax}}}=0.2$ S/cm$^2$, $B_{\text{fac}}=0.25$, $K_{\text{a}}=8$, and $K_{\text{b}}=15$). The $I_{\text{h}}$ kinetics were also faster than in the original model but remained much slower than those of other channels. To allow easier manipulation of the parameters defining the kinetics, the method of Tabata and Ishida (1996) was adopted to implement $I_{\text{h}}$ kinetics. The description is as follows

$$g_{I_{\text{h}}} = g_{I_{\text{hmax}}} S$$

$$\alpha_{I_{\text{h}}} = \alpha_{I_{\text{hmax}}} 0 \exp((V + 62 - I_{\text{SIFa}})/K_{\text{a}})$$

$$\beta_{I_{\text{h}}} = \beta_{I_{\text{hmax}}} 0 \exp(-(V + 62 - I_{\text{SIFb}})/K_{\text{a}}) + 1$$

and the $i_{\text{h}}$ is governed by

$$\tau_{I_{h}} \frac{di_{\text{h}}}{dt} + i_{\text{h}} = i_{\text{h}}$$

and

$$\tau_{I_{h}} = \frac{I_{\text{SIFa}}}{(\alpha_{I_{h}} + \beta_{I_{h}})}$$

$$i_{\text{h}} = \frac{\alpha_{I_{h}}}{(\alpha_{I_{h}} + \beta_{I_{h}})}$$

where $\tau_{I_{h}}$ (in ms) is the time constant for parameter $i_{\text{h}}$ ($i_{\text{h}} \in [0,1]$) and $i_{\text{h}}$ is a function of both time $t$ and membrane potential $V$, in mV). $I_{\text{SIFa}}$ is the value of $i_{\text{h}}$ after the membrane potential is held at a constant level for infinite time, $\alpha_{I_{h}}$ and $\beta_{I_{h}}$ are rate constants and functions of membrane potential only, and $I_{\text{SIFb}}$ is a scaling factor for time constant $\tau_{I_{h}}$, which affect the speed of the kinetics. For the basic parameter set, the equilibrium potential $E_{I_{\text{h}}} = -40$ mV, and $g_{I_{\text{hmax}}}=0.004$ S/cm$^2$; $I_{\text{SIFa}} = 0.25$, $\alpha_{I_{h}} = 0.000001$, $\beta_{I_{h}} = 0.01$, $I_{\text{SIFb}} = 62$ mV, $I_{\text{SIFb}} = -13$ mV, $K_{\text{a}} = -11$, and $K_{\text{b}} = -3.7$. The maximum conductance $g_{I_{\text{hmax}}}$ and the scaling factor $I_{\text{SIFb}}$ were varied during the simulations. Because voltage-clamp data are not available for octopus cells,

FIG. 1. A: schematic representation of the octopus cell model (d, diameter; l, length). B: compartmental representation of the model. Soma and axon are each represented by 1 compartment (box in the figure), whereas each dendrite is divided into 20 sections of equal length and thus represented by the same number of compartments. Compartments are interconnected with resistors. C: details inside each box (compartment). Each compartment contains a membrane capacitor ($c_m$), a leakage branch consisting of a resistor (conductance $g_{\text{leak}}$), and a battery (leakage equilibrium potential $E_{\text{leak}}$). It also may contain other branches ($g_i$-$E_i$) representing ion channels or synaptic inputs.

FIG. 2. Voltage responses of the original octopus cell model (Cai et al. 1997a) to current injections measured at the soma compartment. A: responses of the model when the maximum conductance of the $K_{\text{LT}}$ channels was set to $0.01$ nS/cm$^2$, providing a resting conductance of $31$ nS. Current level was $2$ nA. B: responses of the model when the maximum conductance of the $K_{\text{LT}}$ channels was doubled ($0.02$ nS/cm$^2$). Current level was $2.2$ nA. Current ramps are schematized at the bottom of each panel. In both cases, the ramp times were $1–5$ ms (1-ms steps).
characterization of their ion channels remains qualitative. Therefore the kinetics of the ion channels used in the model are based on data from other cell types. As described in Cai et al. (1997a), the kinetics of \( K_{\text{LT}} \) were modified from those exhibited by type II (bushy) neurons of the ventral cochlear nucleus (Manis and Marx 1991), and those of \( I_h \) were based on data obtained from a variety of other cell types [e.g., Purkinje fibers (DiFrancesco 1981), retinal ganglion cells (Tabata and Ishida 1996), and neurons of the medial nucleus of the trapezoid body of the auditory system (Banks et al. 1993)]. As stated earlier, the maximum conductance of \( K_{\text{LT}} \) was increased considerably in the new model. We intentionally minimized the contribution of the h-type conductance to the resting membrane conductance in the new model as a computational starting point, to isolate the conductance \( (g_{\text{K}_{\text{LT}}} + g_{\text{K}_{\text{p}}}) \) that we thought to be the most important. We then increased gradually the maximum h-type conductance (with or without decreasing the \( K_{\text{LT}} \) conductance) to study the contribution of the two conductances to the responses of octopus cells.

**Auditory-nerve data collection**

Both current injection (simulating in vitro experimental conditions) and spike trains recorded from auditory-nerve (AN) fibers (simulating acoustic stimulation experiments) were used as inputs to the model. Generally, simulated AN spike trains are used as inputs to neuronal models of cochlear nucleus neurons [e.g., Banks and Sachs 1991; Levy and Kipke 1997, 1998]. However, we chose to use experimentally recorded AN spike trains to avoid the oversimplification that typically results from modeling the basilar membrane stage and the inner hair cell synapse stage used to generate simulated AN spikes.

Spike trains from AN fibers of cats using tone burst stimuli were collected as part of a larger study involving harmonic complex stimuli (e.g., Cai et al. 1998), following standard experimental procedures [e.g., Cai and Geisler 1996; Fitzakerley et al. 1994]. Briefly, adults cats ranging from 0.5 to 2 yr of age, born and raised in the animal care facility of this institution, were anesthetized with pentobarbital (40 mg/kg ip), a trachea tube was inserted, and the pinna was removed. A small hole was opened in the skull and cerebellar tissue was aspirated to expose the auditory-nerve. The acoustic system then was calibrated. A glass microelectrode, filled with 2 M KCl and having an impedance of \( \approx 15 \) M\( \Omega \), was inserted into the nerve under visual guidance. A microdrive was used to advance the electrode. When an AN fiber was encountered, a frequency-threshold tuning curve was acquired, and the characteristic frequency (CF) and spontaneous firing rate were determined. Tone bursts were presented to the ear through a Beyer DT-48 dynamic phone. Stimuli, with rise/fall times of 5 ms, durations of 50 ms, and 120-ms repetition intervals, were incremented over an intensity range of 30–70 dB SPL in 5-dB steps and were repeated 50 times at each level. The same set of stimuli and the same stimulus locations on the model: 30 at the soma, 30 at the 5 proximal dendritic compartments, and the remaining 60 at more distal dendritic compartments. The relatively small number of somatic inputs (30) compared with Liberman’s estimate (64) was implemented to promote computational efficiency. Although inputs from each AN fiber may span several compartments, a tonotopical distribution is maintained with inputs from fibers with the highest CFs applied at distal dendritic compartments (Oertel 1997).

To increase the total number of inputs to 120, each spike train has to be applied to multiple (20) locations. However, the temporal order of spike trains recorded from an AN fiber was varied at different input locations. Because each stimulus was presented 50 times (producing 50 trials of spike trains) for each fiber, we varied the number of the starting trial and applied the spike trains in a circular manner (e.g., trials 7, 8, . . . , 50, 1, . . . , 6) to increase the temporal variability. This procedure ensures that no two inputs were identical at a given moment in time even though they originate from the spike trains obtained from the same AN fiber. The rationale for using this approach is based on the observation that each AN fiber makes synaptic contact with an octopus cell at multiple locations (e.g., Kane 1973). Also because each inner hair cell is innervated by multiple different synapses (Spoendlin 1969), spike generation in all AN fibers contacting the same inner hair cell is presumably driven by the same generator potential. Consequently spikes of AN fibers from a common origin are statistically correlated. Our approach simulates this association and compensates for the small number of statistically independent inputs.

**Simulation and analysis**

Simulations were performed on a Pentium-133 PC running a Linux (a PC-based Unix) operating system, using a simulation program developed in our laboratory (Cai et al. 1997b). The program uses a text file to specify the parameters of the model, including the electrical characteristics and the ion channels of each compartment, as well as the connections between compartments and the names and locations of synaptic inputs. The model then is constructed automatically during the simulation based on the parameters in the text file. For each compartment, a partial differential equation is written, and the program solves a system of equations using a modified Crank-Nicholson method with a step size of 10 \( \mu \)s. Synaptic inputs are stored in separate files and are accessed by the program during the simulation. When AN fiber spike trains are used as inputs, the repetition interval is 120 ms, the same as that used during the collection of AN spike train data. Simulations of 50 trials take \( \approx 11 \) min (\( \approx 0.9 \) real time). Action potentials were detected at the axon compartment using a combination of threshold (\( \approx 20 \) mV) and slope (local maxima) criteria. Timing of action potentials, trial-by-trial changes of membrane po-
potentials and ion conductances were stored for later analysis. Post-stimulus time histograms (PSTHs) and interspike interval histograms (ISIHs) also were generated as needed.

To quantify the sensitivity of the octopus cell model to changes in membrane potential during a ramped current simulation, we measured the rate of membrane potential change (mV/ms) before the initiation of an action potential (cf. Figs. 2 and 4A). For each stimulus condition, a derivative function of the soma membrane potential is obtained. There are at least two peaks that can be resolved in the derivative function even when the start of the action potential was not apparent in the membrane potential traces. The first peak occurs before the time an action potential would initiate, and the second peak occurs during the upstroke of the action potential (if an action potential is initiated) or during subsequent potential changes (if an action potential is initiated). The value of the first peak in the derivative function is taken as the rate of membrane potential change by the simulation program. We defined slope threshold as the minimum rate of membrane potential change required to initiate an action potential, using a minimum of 0.1 ms step size for the ramp time when obtaining the slope threshold (see footnote 1).

RESULTS

Figure 3A shows the responses of the model when DC currents were injected into the soma compartment. The model had a threshold of 2.8 nA when current was delivered as a step, consistent with the finding that octopus cells always have a current threshold of ≥2 nA under whole cell clamp condition (Golding et al. 1999). When an above-threshold depolarizing current was used, the model produced an action potential at the stimulus onset followed by membrane depolarization during the steady state. This is typical of responses of octopus cells (Feng et al. 1994; Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data; Golding et al. 1995, 1999). When the injected current was hyperpolarizing, the model produced an initial hyperpolarization followed by a sag toward the resting membrane potential and, depending on the current level, an anode break action potential at the offset of the stimulus. This behavior is typical of octopus cells (Golding et al. 1995, 1999). The current-voltage relationship (Fig. 3B) exhibited strong rectification, that is also similar to findings obtained experimentally (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data; Golding et al. 1995, 1999). In the depolarizing range, the membrane potential changed very little as the level of current was increased. In the hyperpolarizing range, the slope (impedance) was much larger than that in the depolarizing range but was small compared with those from other types of neurons in the cochlear nucleus (Oertel 1983, 1997).

Responses of the model to current ramps

Simulated responses were obtained to ramped currents, which were injected into the soma compartment. Different levels of current were used (3.5, 6, and 9 nA), and each was capable of initiating an action potential when presented as a step. The responses of the model to 6-nA current ramps are shown in Fig. 4A. The model produced action potentials to current ramped over the range from 0.5 to 2.0 ms. However, only subthreshold responses were observed when ramp time was ≥2.5 ms. Because the current injection initiates action potentials when presented as a step, this result suggests that the model is sensitive to the ramp time (or rate of change in membrane potential, see Fig. 4D). Such sensitivity is characteristic of octopus cells (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data). The action potentials, measured at the soma compartment, are brief, measuring only ~0.4 ms at the base. They are also very small in size, measuring no more than 20–30 mV from the resting state or ~20 mV above the steady-state depolarization level. These features are also similar to those observed experimentally (e.g., Golding et al. 1999).

Changes in $K_{LT}$ conductance that correspond to changes in membrane potential during the injection of the ramped current are shown in Fig. 4B. It is clear that the $K_{LT}$ conductance underwent large changes for all ramp times tested, similar to previous results obtained using current steps (Cai et al. 1997a). In particular, for ramp times in which the model failed to produce action potentials, $gK_{LT}$ changed from 120 to ~350 nS, nearly tripling its contribution to the membrane conductance. Such a dynamic change in the $K_{LT}$ conductance increased the overall membrane conductance and thus increased the level of current required to initiate an action potential. As ramp times were shortened (current was delivered faster), the $K_{LT}$ conductance increased at a faster rate, and, as a result, more current was needed to depolarize the membrane. When the current delivery was fast enough to outpace the increase in $K_{LT}$ conductance, an action potential was generated. For long ramp times, it would appear that the current was not delivered at an adequately fast rate (i.e., the ramp was too long) to overcome

![Figure 3](http://jn.physiology.org/DownloadedFromHttp://jn.physiology.org/By/May22017DownloadedFromHttp://jn.physiology.org/)
the dynamic increase in membrane conductance and to produce an action potential.

In contrast, the h-type conductance changed at a much slower pace, and there was virtually no difference in the dynamics of $g_{I_h}$, whether or not an action potential was initiated (Fig. 4C). Although the h-type conductance was minimized intentionally in the parameter set used to produce the responses shown in Fig. 4, the slow time course of changes in $g_{I_h}$ suggests that even when $g_{I_h}$ is large, it is unlikely to significantly influence the transient response of the model.

The interaction between the injected current and the dynamically increased membrane conductance is reflected in the rate that membrane potential subsequently changes. In Fig. 4D, we show the relationship between the rate of membrane potential change and the peak membrane potential relative to the resting potential produced by current injection into the soma compartment. It is clear that a minimum rate of potential change (slope threshold) must be attained before the model neuron produces an action potential. When the rate of potential change is above $\sim 10 \text{ mV/ms}$, an action potential is always evoked, and for faster or slower rates of potential change, an increase in the rate of change in membrane potential resulted in only a slight increase in the peak height of the depolarization or the action potential. As the level of current was increased, the maximum ramp time that can evoke an action potential increased, but the slope threshold, defined as the minimum rate of potential change needed to evoke an action potential, did not change. For all three current levels used (3.5, 6, and 9 nA), the slope threshold was $\sim 10 \text{ mV/ms}$. Such independence of the slope threshold on the level of injected current has also been observed in experimental studies (Ferragamo and Oertel 1998, unpublished data).1

![Fig. 4.](http://jn.physiology.org/)

**Effects of increasing the h-type conductance**

To further study the roles of $K_{LT}$ and $I_h$ in shaping the octopus cell’s responses and particularly its sensitivity to changes in membrane potential, the relative proportion of the $K_{LT}$ and the h-type conductances was varied. In the first set of manipulations, we replaced part of $K_{LT}$ conductance with h-type conductance: the reduction of $K_{LT}$’s contribution to the resting membrane conductance was balanced by that of $I_h$, thus

1 Such independence of slope threshold on stimulus level is relative and does not hold for stimuli that are very short or near current threshold at least in our simulations. Under those conditions, a faster rate of potential change is need to initiate an action potential.

As shown in Fig. 4D, although the rate of change in membrane potential ($dv/dt$) changed continuously, the peak membrane potential jumped as the rate of change in membrane potential was increased. The jump occurred at about the same membrane potential for different levels of stimuli. A possible explanation is that a certain membrane potential level must be reached before the spiking channels (mainly the Na$^+$ channel in the axon compartment) open and initiate an action potential. However, whether that membrane potential level can be reached is controlled by other factors, which are reflected in the $dv/dt$ measure. By changing the kinetics of the Na$^+$ channel in the axon compartment, we were able to change the membrane potential at which the jump occurs during simulation. Thus the use of the term “slope threshold” is not intended to reflect the underlying mechanism and should not be interpreted as such.
keeping the resting membrane conductance constant. When the contribution of the h-type conductance to the resting membrane conductance was increased (and that of \( K_{LT} \) conductance was decreased), the current threshold (measured using step currents) decreased slightly, from the original 2.8 to 2.1 nA when 75% \( K_{LT} \) was replaced. More significantly, the minimum rate of potential change required to initiate action potentials (slope threshold) decreased, for all current levels (Fig. 5A). When 25% of \( K_{LT} \) was replaced, the slope threshold began to show dependence on the level of current used, i.e., at higher levels, a smaller rate of change was required to initiate an action potential. Such dependence was more obvious when \( \leq 50\% \) of \( K_{LT} \) was replaced. When 75% of \( K_{LT} \) was replaced and a 9-nA current injection was simulated, the model neuron produced action potentials regardless of ramp time (\( \leq 50 \text{ ms} \)). This suggests that spike production by the modified model was not sensitive to the rate of potential change induced by the current. Consequently, its slope threshold is near zero (Fig. 5A). Membrane potential changes in the soma compartment following the injection of 6- and 9-nA currents (4-ms ramp time) are shown in Fig. 5, B and C, respectively. When 50% of the \( K_{LT} \) conductance was replaced with the h-type conductance, the model neuron produced a single action potential with a 6-nA current (Fig. 5B, —) and two action potentials with a 9-nA current (Fig. 5C, —). However, when 75% of the \( K_{LT} \) conductance was replaced with the h-type conductance, five action potentials were produced in the first 20-ms time period when stimulated with a 6-nA current (Fig. 5B, - - -), making the responses of the model neuron more “chopper-like” under these conditions. When the current level was increased to 9 nA, the model responded with a sustained chopping pattern (Fig. 5C, - - -). The effect of replacing \( g_{K_{LT}} \) with \( g_{h} \) also is reflected in the slight increase in the width of action potentials generated by the model (Figs. 4, and 5, B and C). It should be noted that repetitive firing is not observed when \( K_{LT} \) is blocked partially by 4-AP, and the width of the action potential increases dramatically after the \( K_{LT} \) blockage (Golding et al. 1999). These differences might be attributed to a voltage-dependent \( C^{2+} \) channel (which was not included in the model, see DISCUSSION). The much higher currents used in the simulation might also be partially responsible for the repetitive firing. Under these conditions, the Hodgkin-Huxley type Na⁺ and K⁺ channels in the axon and soma compartments become the dominant factor in determining the model neuron’s response, thus generating a chopping pattern similar to those of stellate cells (Banks and Sachs 1991). Nonetheless the decreased slope threshold and the increased tendency of firing multiple spikes after \( g_{K_{LT}} \) was replaced by \( g_{h} \) further support the idea that \( K_{LT} \) is important to the octopus cell’s sensitivity to the rate of change in membrane potential and that \( I_{h} \) contributes little to this aspect of the octopus cell’s response.

Because an increase of h-type conductance always is accompanied by a decrease in \( K_{LT} \) conductance in the h-type conductance substitution experiment, it is unclear whether the change in response is due to increased \( g_{I} \) or decreased \( g_{K_{LT}} \), as both are varied simultaneously. To address this question, we examine the model’s responses when \( g_{I} \) is increased while maintaining constant \( g_{K_{LT}} \). Note that a side effect of this manipulation is that the overall membrane conductance is increased.

In Fig. 6A, we show the slope threshold as a function of the ratio of \( g_{h} \) and \( g_{K_{LT}} \) at rest, when the resting \( K_{LT} \) conductance was 120 (——) and 60 nS (—). It is clear that the slope threshold only decreased slightly over a relatively wide range of \( g_{I}/g_{K_{LT}} \) ratios. In contrast, there was a significant decrease in slope threshold when the resting \( K_{LT} \) conductance was changed from 120 to 60 nS over the same \( g_{I}/g_{K_{LT}} \) range. Consistent with results in Fig. 5A, the slope threshold also showed dependence on current level when the \( K_{LT} \) conductance was decreased (— - -). When the resting \( K_{LT} \) conductance was maintained at 120

![Image](http://jn.physiology.org/)

**FIG. 5.** A: slope thresholds (minimum rates of membrane potential changes required to initiate action potentials) as a function of the percentage of the \( K_{LT} \) conductance replaced by h-type conductance. Overall resting membrane conductance was kept constant. B: membrane potential changes in the soma compartment in response to a 6-nA current injection to the soma compartment with a ramp time of 4 ms. —, 75% of the \( K_{LT} \) conductance was replaced by h-type conductance. - - - , 75% was replaced. C: same as in B except that a 9-nA current was used.
When the resting current level (maximum current used was 15 nA), size and width of the action potential are observed in both size and width of the action potential are observed. However, regardless of the value of the h-type conductance and the \( g_{K_{LT}} \) ratio, slope thresholds as a function of the ratio of resting \( g_{I_h} \) and \( g_{K_{LT}} \). This threshold was measured using current steps.

**Figure 6.** A: slope thresholds as a function of the ratio of resting \( g_{I_h} \) and \( g_{K_{LT}} \). Resting \( K_{LT} \) conductance was kept constant at 120 nS (---) or 60 nS (−−−). A resting h-type conductance of 120 nS was achieved by setting \( g_{I_{max}} \) to be 0.133 S/cm². B: current threshold as a function of the ratio of resting \( g_{I_h} \) and \( g_{K_{LT}} \). This threshold was measured using current steps.

nS, the single action potential pattern always was maintained regardless of the value of the h-type conductance and the current level (maximum current used was 15 nA). However, when the resting \( K_{LT} \) conductance was reduced to 60 nS, multiple action potentials were elicited for currents 9.2–11 nA, depending on the value of h-type conductance. Even though the increased overall membrane conductance was a complicating factor in this manipulation, the relative small change in slope threshold over a relatively wide range of \( g_{I_h}/g_{K_{LT}} \) ratios as well as the decreased slope thresholds and increased tendency of multiple firing when resting \( K_{LT} \) conductance was changed from 120 to 60 nS, support the idea that the decrease in slope threshold and the multiple firing observed in the h-type conductance substitution experiment (Fig. 5A) are mainly due to the decrease in \( K_{LT} \) conductance not the increase in h-type conductance. Thus \( K_{LT} \) is the key to the octopus cell’s sensitivity to changes in membrane potential and its transient responses.

Although a wide range in h-type conductance does not affect the slope threshold, the h-type conductance does affect the absolute threshold (when current was injected as a step; Fig. 6B), especially when the \( K_{LT} \) conductance is 120 nS at rest. As the \( g_{I_h}/g_{K_{LT}} \) ratio increases, the current threshold also increases presumably due to the increase in overall membrane conductance. The value of the h-type conductance also affects size and width of the action potential. As \( g_{I_h} \) increases, reductions in both size and width of the action potential are observed that are consistent with the increase in size and width observed when \( I_h \) was blocked by Cs⁺ (Golding et al. 1999). The exact amounts depend on \( g_{I_h} \) and \( g_{K_{LT}} \) and kinetics of \( K_{LT} \) and \( I_h \). For example, when the \( K_{LT} \) conductance is 120 nS at rest and the resting h-type conductance was increased from 4 to 120 nS, the size and the width of the action potential decreased by \( \frac{1}{4} \) and \( \frac{1}{5} \), respectively. In general, factors that increase the membrane conductance can reduce the size and the width of the action potential.

**Effects of replacing the \( K_{LT} \) conductance with a leakage conductance**

To address the question whether the \( K_{LT} \) conductance can be replaced with a static (leakage) conductance, we gradually replaced the \( K_{LT} \) conductance with a membrane leakage conductance while keeping the resting membrane conductance constant, again using the slope threshold as the metric of sensitivity. As shown in Fig. 7, the results are similar to those observed when \( K_{LT} \) conductance was replaced by the h-type conductance. In fact, they are almost identical. The current threshold also decreased slightly as the \( K_{LT} \) conductance was replaced with a leakage conductance. In addition, multiple spikes were evoked when \( \geq 50\% \) of \( K_{LT} \) conductance was replaced with a leakage conductance and current levels were \( \geq 6 \) nA. Similarities such as these are not surprising when one considers the slow kinetics of the h-type conductance and the short ramp time implemented in these simulations (usually \( <10 \) ms). These results suggest that \( K_{LT} \) not only contributes to the low membrane resistance but, more importantly, dynamically regulates the cell’s response to inputs. Such a dynamic role cannot be provided by a static leakage conductance.

**Effect of the speeds of \( K_{LT} \) and \( I_h \) kinetics**

Figure 8A shows the slope threshold as a function of \( B_{lec} \) (the scaling factor that controls the \( K_{LT} \) kinetics), using the basic parameters described in METHODS. Larger \( B_{lec} \) (corresponding to slower \( K_{LT} \) kinetics) yielded lower slope thresholds. As channel kinetics speed up (\( B_{lec} \) smaller), slope thresholds increased. It
Role of ion conductances in octopus cell responses

Simulation of acoustical stimulation

Although the model produces realistic responses to simulated current stimulation, it is very important that the model also faithfully reflect in vivo responses to “acoustic stimulation.” In this section, we examine the model’s responses to spike trains of auditory-nerve fibers recorded experimentally using tone burst stimulation.

When the spike trains recorded in response to a 500-Hz tone burst served as inputs to the model, the model neuron responded with a threshold of 60 dB SPL and phase-locked to the input signal, as is evident in the PSTH at 70 dB SPL (Fig. 9A). Such spike entrainment is typical for octopus cells at low stimulus frequencies (up to a maximum frequency of 500–2,000 Hz) (Godfrey et al. 1975; Rhode and Greenberg 1992). At higher stimulus frequencies, octopus cells usually respond to stimuli with a major onset peak in the PSTH. Depending on the steady-state discharge activity, the PSTHs exhibit O1 (little or no steady-state response) or O2 (steady-state response >10 spikes/s) profiles. Both types of PSTH patterns have been observed from physiologically characterized and morphologically identified octopus cells (Feng et al. 1994; Rhode et al. 1983; Rouiller and Ryugo 1984). When the stimulus frequency was 1,000 Hz, the same model system, with no change in parameters, responded at stimulus onset only (Fig. 9, B–D).

Little steady-state activity was produced during the 50-ms stimulus duration when the stimulus level was incremented from threshold at this frequency (35 dB SPL) to 70 dB SPL. This response pattern is classified as an O1 response. As the stimulus level was increased, the latency of the responses also decreased. These characteristics are similar to those observed experimentally and suggest that the model functions realistically under a variety of conditions.

The changes in the response of the model neuron to acoustic stimulation when a large portion of the $K_{LT}$ conductance was replaced by the h-type conductance are shown in Fig. 10. The same AN fiber spike trains collected using a 1,000-Hz tone at 70 dB SPL (cf. Fig. 9D) were used as inputs to the altered model. When the $K_{LT}$ conductance was replaced gradually by the h-type conductance, spikes began to appear during the steady state, and also a second peak emerged after the initial onset peak. When 75% of the $K_{LT}$ conductance was replaced, there was substantial activity during the steady state and the second response mode was observed. Response patterns like these are classified as O2 (onset chopper), and typically are produced by large multipolar stellate cells in the PVCN (Smith and Rhode 1989). Such O2 PSTH response patterns are also consistent with the multiple spike pattern obtained under current stimulation when significant portions of the $K_{LT}$ conductance are replaced by the h-type conductance (Fig. 5, B and C).

When the h-type conductance was increased and the $K_{LT}$ conductance was unchanged, the model maintained its onset response pattern; however, the threshold was increased (by ~15 dB at 1,000 Hz), as might be expected, due to the increase in overall resting membrane conductance. Figure 11 shows the response of the model neuron when the resting h-type conductance equals the resting $K_{LT}$ conductance. To achieve a similar response threshold to acoustic stimulation, we increased individual synaptic conductance by 25% to 4.6 nS ($G = 12.5$). It is clear that the model responses to both 500- and 1,000-Hz tone bursts are very similar to those before the increase of the h-type conductance (cf. Fig. 9). This result, together with those in Figs. 9 and 10, suggest that realistic PSTH response patterns can be simulated as long as a large $K_{LT}$ conductance is incorporated in the model.
Fig. 9. Poststimulus histogram (PSTH) responses of the model to experimentally recorded spike trains of auditory-nerve fibers. A: 500-Hz, 70 dB SPL tone bursts were used to collect the spike train data. Model showed entrainment to the stimulus. B–D: 1,000-Hz tone bursts presented at 40, 50, and 70 dB SPL. In this and the next 2 figures, only 60 ms of the 120-ms responses are shown. Portions not shown contained no spikes. Binwidth of all histograms is 0.5 ms. For all panels, stimulus duration was 50 ms.

Fig. 10. Responses of the model to 1,000 Hz, 70 dB SPL tone bursts when part of the $K_{LT}$ conductance was replaced by h-type conductance. Top: 50% of $gK_{LT}$ was replaced by $g_{Ih}$ ($g_{Ih_{\text{max}}} = 0.067 \text{ S/cm}^2$); bottom: 75% was replaced ($g_{Ih_{\text{max}}} = 0.1 \text{ S/cm}^2$). A 2nd prominent response mode appeared in the PSTHs (A and C), and discharge rate increased during the steady state. Corresponding interspike interval histograms (ISIHs) are shown in B and D.
Contributions of the $K_{LT}$ and the h-type conductances

$K_{LT}$ appears to be the main contributor to the octopus cell’s response characteristics. In this study, we implemented a computer model to simulate the responses of octopus cells and focused on sensitivity to the rate that membrane potential changes after ramped current stimulation and on the temporal response properties produced by acoustic stimulation. Our simulations suggest that $K_{LT}$ is an important factor underlying the octopus cell’s sensitivity to the rate of change in membrane potential under current stimulation conditions. When an otherwise sufficient amount of current is delivered to the model neuron over a relatively long time, the model fails to initiate an action potential (Fig. 4). This is, presumably, the consequence of a fast $K_{LT}$ activation, i.e., the concomitant increase in $K_{LT}$ conductance increased the overall membrane conductance and thus the amount of current required to initiate an action potential. When the $K_{LT}$ conductance was decreased, with (Fig. 6A also Fig. 2) or without a change in the overall resting membrane conductance (Fig. 5), the sensitivity of the model neuron to the rate that membrane potential changes decreases. This finding is similar to the effect produced by blocking $K_{LT}$ with $\alpha$-dendrotoxin and 4-AP (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data).

When spike trains of auditory-nerve fibers were used as inputs to the model (to simulate acoustic stimulation), the model produced realistic onset PSTH patterns (Figs. 9 and 11) when a large $gK_{LT}$ was maintained, regardless of the value of $g_{I_{h}}$. Replacing part of the $K_{LT}$ conductance with the h-type conductance changed the response pattern from $O_{I}$ to $O_{C}$-like (Fig. 10). These results support the conclusion that the $K_{LT}$ conductance is the principal conductance underlying the onset response characteristics of the octopus cell and that it underlies the cell’s sensitivity to changes in membrane potential. These results, together with the experimental finding that $K_{LT}$ is the major conductance operating during steady-state depolarization (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data; Golding et al. 1999), lead to our conclusion that $K_{LT}$ is the most important factor shaping the octopus cell’s response properties.

Previously we showed that doubling the h-type conductance in the model produced multiple spikes at stimulus onset when $gK_{LT}$ was relatively small (Cai et al. 1997a). In this study, we extended that finding and demonstrated that when $K_{LT}$ contribution is relatively low, the sensitivity of octopus cells to the rate that membrane potential changes after stimulation is decreased, resulting in multiple spikes (chopping pattern) under current stimulation conditions (Fig. 5) and $O_{C}$-like PSTH patterns under acoustic stimulation conditions (Fig. 10). It follows from this finding that the contribution of $K_{LT}$ to the resting membrane conductance may be less significant in large multipolar stellate cells (which show $O_{C}$ responses) than in octopus cells.

$K_{LT}$ and $I_{h}$ operate in different membrane potential ranges. Because $K_{LT}$ is activated during depolarization and $I_{h}$ is activated during hyperpolarization, both are active in octopus cells, but they operate in different ranges. In the depolarizing range, the $K_{LT}$ conductance dominates the mem-

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**Fig. 11.** PSTH responses of the model to experimentally recorded spike trains of auditory-nerve fibers when the h-type conductance was increased, while the $K_{LT}$ conductance was held constant at 120 nS. This figure was organized in the same way as Fig. 9, and so were the basic model parameters, including the application of synaptic inputs. Only differences are an increased h-type conductance ($g_{I_{h_{max}}}$ = 0.133 S/cm², which yields a resting $g_{I_{h}}$ of 120 nS, same as that of $K_{LT}$) and an increased synaptic conductance (4.6 nS). A: 500-Hz, 70 dB SPL tone bursts were used to collect the spike train data. Model showed entrainment to the stimulus. B–D: 1,000-Hz tone bursts presented at 40, 50, and 70 dB SPL.
brane conductance, which is consistent with the data of Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data. In the hyperpolarizing range, the h-type conductance dominates the membrane conductance, which is consistent with the data of Golding et al. (1995, 1999).

Possible role of \( I_h \). Because there is no strong evidence suggesting the existence of inhibitory inputs on octopus cells (Golding et al. 1995; Saint Marie et al. 1991; Wenhold et al. 1986, 1987; Wier et al. 1991), it is reasonable to conclude that octopus cells operate mainly in the depolarizing range under normal physiological conditions, thus limiting the role that \( I_h \) plays in shaping octopus cell response properties. This is also consistent with simulation results showing that the basic onset responses of octopus cells (both intracellular under current stimulation or in vivo under acoustic stimulation) do not require a substantial \( I_h \) contribution (Figs. 3, 4, and 9).

However, available experimental data suggest that h-type conductance may contribute significantly to the high membrane conductance of octopus cells (Golding et al. 1995, 1999). Our simulations suggest that although \( I_h \) does not have a significant influence on the transient responses of octopus cells (Figs. 6 and 11), the level of the contribution of the h-type conductance to the membrane conductance does significantly affect the model neuron’s thresholds to both current stimulation (Fig. 6B) and acoustic stimulation. It is possible that a significant contribution of this conductance to the low-resistance environment allows it to play a role in the long-term regulation of the cell’s metabolic state. If, for example, under the influence of metabotropic agents, the kinetics of \( I_h \) change so that the resting h-type conductance increases or decreases, the contribution of \( I_h \) could regulate the sensitivity of the neuron through its influence on response threshold and thus affect the ability of the neuron to process complex stimuli. Evidence already exists that suggests inward rectifier currents are regulated metabotropically in neurons of the auditory and other systems (Banks et al. 1993; Dixon and Copenhagen 1997; Ingram and Williams 1996; Wang and Robertson 1998).

Role of a low membrane resistance and synaptic inputs

There is no doubt that a low membrane resistance (large membrane conductance) is important in octopus cell responses. This is supported by both experimental findings (Ferragamo and Oertel 1998; Ferragamo and Oertel, unpublished data; Golding et al. 1995, 1999) and computational simulations that implement low membrane resistance as their main feature (Cai et al. 1997a; Evans 1998; Levy and Kipke 1997). Because of this low membrane resistance, octopus cells require highly synchronized inputs to produce an action potential (i.e., “coincidence detection”). Individual synaptic inputs evoke small, brief synaptic events that are generally insufficient to trigger an action potential (Golding et al. 1995). However, a low membrane resistance alone produces realistic responses under only limited conditions (Cai et al. 1997a; Evans 1998). In this study, when \( K_{LT} \) conductance was replaced by a leakage conductance, the model neuron exhibited decreased sensitivity to the rate of change in membrane potential (Fig. 7) and generated multiple action potentials instead of a single action potential when current injection was simulated. These results suggest that \( K_{LT} \) plays a dynamic role in the responses of octopus cells. The dynamic increase in conductance generated by ion channel(s) to maintain a low-resistance environment (relative to the strength of the stimulus) is more important than a large static leakage conductance especially at higher stimulus levels.

Theoretically, such a dynamic role can be provided by other conductances (e.g., the Hodgkin-Huxley type \( K^+ \) channel). For example, the \( K^+ \) channel, like the \( K_{LT} \), is also activated on depolarization and is not inactivating. Its conductance undergoes large changes during the action potential in a manner similar to \( K_{LT} \) conductance and part of the effect is maintained during the steady-state responses (cf. Fig. 6 of Cai et al. 1997a). In our model, the maximum \( K^+ \) conductance is small, making its contribution to the overall membrane conductance very small. In the Levy-Kipke model (Levy and Kipke 1997, 1998), \( K_{LT} \) is not included but the maximum \( K^+ \) conductance is large. As a result, the \( K^+ \) channel might have played a similar role in their model as \( K_{LT} \) plays in our model.

Recently Levy and Kipke (1998) emphasized the importance of synaptic effectiveness (the ratio of the synaptic conductance to the leakage conductance) and dynamic spike threshold as factors shaping octopus cell responses. According to them, thresholds are low at stimulus onset but increase as the membrane is depolarized during the steady-state, resulting in a decrease in synaptic effectiveness. We agree with this general explanation but offer an alternative mechanism for its underlying basis. In both the Kipke and Levy (1997) model and our model, increasing synaptic strength increases steady-state firing rate, producing \( O_t \) responses instead of \( O_p \) patterns. Further increases in synaptic strength result in an increase in spontaneous firing rate and produce responses that are not observed experimentally in octopus cells. Our simulation results suggest that the basis for the decreased synaptic effectiveness and increased threshold during the steady state is the dynamic increase in membrane conductance, which in turn is due to the kinetics of the \( K_{LT} \) channel (Fig. 4).

Model parameters

Ion channels and their kinetics. As partly demonstrated in the simulation results, the model neuron produces onset responses over a wide range of model parameters under both current or acoustic stimulation conditions, although the onset PSTH pattern is more tolerant to parameter changes than is the slope threshold measurement. We do not claim that this model fully represents the biophysical basis of octopus cell function. This is largely the consequence of the fact that many of the octopus cell’s characteristics, especially the kinetics of ion channels, are not known. As a result, assumptions made in this study about channel kinetics were based on characteristics of the same ion channels that have been studied in other cell types in the auditory system or elsewhere. Additionally, some channels that are known to be expressed in octopus cells were not incorporated into our model because too little is known about their relative role(s) during activation. For example, the experimental data of Golding et al. (1999) suggest the existence of a relatively slow, voltage-sensitive \( Ca^{2+} \) channel that is activated in a depolarizing range that is higher than for \( K_{LT} \). Because this conductance does not contribute significantly to the membrane conductance, its influence on the transient response of octopus cells must be limited. This channel, if implemented, should serve to suppress the repetitive firing and dramatically broaden the width of action potentials in our
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model when \( K_{\text{LT}} \) conductance is replaced by h-type conductance (Fig. 5).

On the basis of the simulation results illustrated in Figs. 5, 6, and 11, it is reasonable for \( I_h \) to contribute significantly to the resting membrane conductance of octopus cells, possibly in the amount of some 50–100% of the contribution of \( K_{\text{LT}} \). Such a contribution by \( I_h \) is more consistent with the experimental data of Golding et al. (1999) in which it was shown that membrane impedance is increased when \( I_h \) is blocked although to a lesser extent in the depolarizing direction than in the hyperpolarizing direction. As a result, the maximum h-type conductance must be increased, and other parameters governing \( I_h \) kinetics also need to be adjusted accordingly to match experimentally recorded responses of octopus cells mainly under hyperpolarizing conditions. The half-activation point of \( I_h \) also may need to be shifted slightly toward the depolarizing direction (by increasing \( I_{\text{hSFR}} \)) to increase the influence of \( I_h \) during depolarization. The increase in current threshold resulting from an increase in the resting contribution of \( I_h \) may be accounted for by differences in the geometric dimensions between the model neuron and a typical mouse octopus cell.

It also should be pointed out that the kinetic characteristics of the h-type conductance implemented in this model are faster than those in the original model. This was implemented to produce a sag during hyperpolarization that is comparable with that observed in experimental data (Fig. 3). However, in all neuron types studied thus far, the h-type conductance generally has slower kinetics than those specified here, although the values vary considerably among neuronal types (e.g., Banks et al. 1993; DiFrancesco 1981; Tabata and Ishida 1996). Although it is possible that the parameters used in our model accurately reflect the properties of the h-type conductance present in octopus cells, this question, together with those concerning other ion channels and their dynamics, can be answered only through experimental studies.

MEMBRANE CONDUCTANCE AND MEMBRANE TIME CONSTANTS. Our model produces realistic responses to both current stimulation and acoustic stimulation even when tested over a wide range of resting membrane conductances. This is not surprising because the events that occur after stimulus onset are largely determined by the dynamics of ion channel(s), particularly \( K_{\text{LT}} \). To maintain high energy efficiency and/or sensitivity to low-level stimuli, it is desirable to have a relatively small resting membrane conductance (or a relatively large resistance) although the exact value may be large in comparison to other types of neurons.

In experimental studies, the membrane time constant usually is estimated from the time course of membrane potential changes in response to a large hyperpolarizing current. Because octopus cells have unusual characteristics and because they primarily operate in the depolarizing range in vivo, one may not be able to accurately estimate the resting membrane resistance from the membrane time constant, although a short membrane time constant may still imply a low resting membrane resistance.

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