Mechanisms of onset responses in octopus cells of the cochlear nucleus: Implications of a model

Yidao Cai, Edward J. Walsh and JoAnn McGee

Developmental Auditory Physiology Laboratory, Boys Town
National Research Hospital, Omaha, Nebraska 68131, USA

Manuscript # J-0007-7

Abbreviated title: Mechanisms of onset responses in octopus cells

Correspondence to:
Yidao Cai
Boys Town National Research Hospital
555 North 30th Street
Omaha, NE 68131
USA
TEL: 402-498-6526
FAX: 402-498-6351
Email: caiy@boystown.org

Abstract

The octopus cells of the posteroventral cochlear nucleus receive inputs from auditory-nerve fibers and form one of the major ascending auditory pathways. They respond to acoustic and electrical stimulation transiently, and are believed to carry temporal information in the precise timing of their action potentials. The mechanism whereby onset responses are generated is not clear. Proposals aimed at elucidating the mechanism range from neural circuitry and/or inhibition, "depolarization block" (or inactivation of Na^+ channels), and the involvement of a 4-AP sensitive, low-threshold channel (K_{LT}). In the present study, we used a compartment model to investigate possible mechanisms. The model cell contains a soma, an axon and four passive dendrites. Four kinds of ionic channels were included in the soma compartment: the Hodgkin-Huxley like Na^+ and K^+ channels, a 4-AP sensitive, low-threshold channel, K_{LT}, and a Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h. DC currents and halfwave-rectified sinewaves were used as stimuli. Our results showed that an onset response can be generated in the absence of neuronal circuitry of any form, thus suggesting that the onset response in octopus cells is regulated intrinsically. Among the many factors involved, low input impedance, partly contributed by I_h, appears to be essential to the basic onset response pattern; also, the K_{LT} conductance plays a major role, while the inactivation of Na^+ channels probably plays only a secondary role. The dynamics of I_h can also modify the response pattern, but due to its slow kinetics, its role is probably limited to longer-term regulation under the conditions simulated in this study.

Key words: mechanism, onset response, octopus cell, cochlear nucleus, model, depolarization block

Introduction

Octopus cells lie in a distinct region within the posteroventral cochlear nucleus (PVCN) known as the octopus cell area (OCA) (Osen, 1969; Kane, 1973; Bawer et al., 1974). They have relatively large cell bodies and thick dendrites which taper slightly in the proximal-distal dimension, distinguishing them from other cell types in the cochlear nuclei (Kane, 1973, 1974; Morest et al., 1973; Rhode et al., 1983; Oertel et al., 1990; Ostapoff et al., 1994; Golding et al., 1995). Inputs from auditory-nerve fibers spanning a relatively wide range of characteristic frequencies converge onto octopus cells, and their outputs project through the intermediate acoustic stria contralaterally to the dorsal-medial periolivary nucleus and the ventral nucleus of the lateral lemniscus, forming one of the major ascending auditory pathways (Warr, 1969, 1972, 1982; Adams and Warr, 1976; Smith et al., 1993). Although the specific functions of such cells are not known, they are thought to carry temporal information in the precise timing of action potentials (Godfrey et al., 1975). Since it has been suggested that the timing of the action potentials underlies the perception of pitch, octopus cells probably contribute to pitch perception (Oertel, 1991; Golding et al., 1995; Rhode, 1995).

Octopus cells produce onset responses to acoustical and electrical stimuli: i.e., under conditions of continuous acoustic stimulation, they show a major peak near the time of stimulus onset in the post-stimulus time histogram (PSTH) (Kiang et al., 1973; Godfrey et al., 1975; Rouiller and Ryugo, 1984; Rhode and Smith, 1986a) and sustained depolarization in intracellular recordings *in vivo* (e.g. Feng et al., 1994); with current injection, they usually fire one action potential at the stimulus onset, followed by sustained depolarization (e.g., Romand, 1978; Feng et al., 1994). These two forms of onset responses (i.e., the onset action potential under current stimulation and the onset PSTH pattern under acoustic stimulation) are related, as it has been shown that both can be recorded from the same octopus cells (Feng et al., 1994; Ostapoff et al., 1994). While there are other cell types in the cochlear nuclei (e.g. the multipolar cell and the fusiform cell) showing onset responses (Rhode et al., 1983; Rhode and Smith, 1986a, 1986b; Smith and Rhode, 1989; Friauf and Ostwald, 1988), the correspondence between octopus cells and the onset response pattern has been established by structural and functional correlation (Godfrey et al., 1975) and by combined anatomical and physiological

studies using labeling techniques, both *in vivo* (Rhode et al., 1983; Rouiller and Ryugo, 1984; Feng et al., 1994; Ostapoff et al., 1994) and in brain slice preparations (Golding et al., 1995).

The mechanisms underlying the production of the onset response pattern in octopus cells, however, are not clear. An obvious possibility is that it might be due to neural circuitry involving interneuron(s). But this has been virtually excluded from consideration based on the short latency of responses (Kane, 1973; Godfrey et al., 1975; Ritz and Brownell, 1982). The observation that a single auditory-nerve fiber can give rise to two types of synaptic endings on a single octopus cell (Kane, 1973; cf., footnote 3) raised the possibility of an interaction between excitatory and inhibitory effects, in which the inhibitory inputs were provided by the thin auditory-nerve fiber collaterals (Kane, 1973; Morest et al., 1973; Godfrey et al., 1975). Immunostaining studies indicated that inhibitory neurotransmitters are present in synapses located at the soma and proximal dendrites of octopus cells in cats (GABA: Adams and Mugnaini, 1987; Saint Marie et al., 1989) and guinea pigs (glycine: Wenthold et al., 1988), and in the PVCN of cats (glycine: Wenthold, 1987) and guinea pigs (GABA: Wenthold et al., 1986; GABA and glycine: Wenthold et al., 1987). However, GABA staining was usually weaker in the PVCN than in other parts of the cochlear nuclei (Wenthold et al., 1986), and glycine staining was weak or even absent in the PVCN (Altschuler et al., 1986; Wenthold et al., 1987; Saint Marie et al., 1991). In mice, inhibitory postsynaptic potentials have been shown to be present in other cell types in the cochlear nuclei, however, none have been recorded in octopus cells (Wu and Oertel, 1986; Hirsch and Oertel, 1988; Golding et al., 1995).

More recently, attention has focused on the intrinsic properties of octopus cells. There have been suggestions (Ritz and Brownell, 1982; Feng et al., 1994) that the onset response is due to the inactivation of Na^+ channels (Hodgkin and Huxley, 1952a), or "depolarization block". Since an octopus cell receives inputs from many auditory-nerve fibers, the multiple inputs maintain the cell in a depolarized state after the initial spike, thus inactivating the voltage-sensitive Na^+ channels and preventing the cell from firing additional spikes. Intracellular recordings indeed show sustained depolarization under either acoustical stimulation (Feng et al., 1994) or current injection (Romand, 1978; Feng et al., 1994), but it is unclear whether the Na^+ channel is inactivated under those conditions. Another suggestion (Feng et al., 1994)

implicates the 4-AP sensitive, low-threshold K^+ channel (K_{LT}), a channel that is similar to that found in type II neurons of the ventral cochlear nucleus (Manis and Marx, 1991), in neurons of the medial nucleus of the trapezoid body (MNTB) (Banks and Smith, 1992), and that is also present in octopus cells (Golding et al., 1995). As intracellular recordings from octopus cells are complicated by low input impedance (Golding et al., 1995), we have implemented a compartment model to test the above hypotheses, with the intention of gaining insight into the mechanism by which onset responses are generated in octopus cells.

Methods

1. The octopus cell model

The octopus cell model used in this study was based on available anatomical and physiological data (Kane, 1973, 1974; Schwartz and Kane, 1977; Rhode et al., 1983; Rhode, 1985; Oertel et al., 1990; Golding et al., 1995). As schematized in Fig. 1A, the model cell has a soma, an axon, and four identical dendrites. We chose a soma diameter of 32 μm, which is about the lower-median for cats and upper boundary for mice. Given the fact that there is no evidence suggesting major differences in axon morphology of different neuron types in the cochlear nucleus, we modeled the axon as in the stellate cell model of Banks and Sachs (1991) (i.e., 3 μm in diameter and 70 μm in length). This axonal model is not intended to represent the entire axon in an octopus cell. Dendrites were modeled as cylinders for simplicity, each being 200 μm in length and 5 μm in diameter, even though the dendrites of octopus cells taper slightly (Kane, 1973, 1974; Morest et al., 1973; Schwartz and Kane, 1977; Rhode et al., 1983; Oertel et al., 1990; Ostapoff et al., 1994; Golding et al., 1995).

The basic electrical parameters of the model were chosen within the widely accepted ranges measured for various cell types and adjusted to fit available physiological data. Specifically, the membrane capacitance density (C_m) was set to 1 $\mu F/cm^2$, which is typical for cell membranes (Jack et al., 1983). The membrane time constant (τ_m) was set to 1 ms, consistent with values observed in slice preparations (Golding et al., 1995). Consequently, the membrane resistivity (R_m) was calculated to be 1 $k\Omega \cdot cm^2$, which is in the lower bound of standard values (Jack et al., 1983). We selected an axial resistivity (R_i) of 100 $\Omega \cdot cm$, a value

that is standard in such cell models (Jack et al., 1983). As will be shown, these basic electrical parameters, together with the morphological parameters, determine other passive electrical parameters used in the model.

While there is increasing evidence suggesting that dendrites can be active and active dendrites play important roles in neuronal signal processing (e.g. Wilson, 1995; Lipowsky et al., 1996; see Cai et al., 1997 for review), we chose to model the dendrites as passive, for simplicity. The dendrites have a space constant (λ) of 354 μm (the electrotonic length, i.e., the length expressed in terms of the space constant, is 0.565). Each dendrite is divided into 20 compartments (Fig. 1B). Thus, each compartment is 10-μm long, with an electrotonic length of 0.0282. On the other hand, the soma and axon contain active channels and are each represented by a single compartment.

In addition to the Hodgkin-Huxley type Na^+ and K^+ channels (Hodgkin and Huxley, 1952b), there are two other major types of ionic conductances in octopus cells: a 4-AP sensitive K^+ channel, K_{LT}, and a Cs^+-sensitive conductance, I_h (Golding et al., 1995). The latter is a hyperpolarization-activated inward rectifier and is responsible for the low input impedance of this neuronal type. It bears resemblance to the I_h found in a variety of other cell types (e.g., in Purkinje fibers, DiFrancesco, 1981; in thalamic relay neurons, McCormick and Pape, 1990; and in retinal ganglion cells, Tabata and Ishida, 1996), including MNTB neurons (Banks et al., 1993). Since there is no quantitative data characterizing the kinetics of channels in octopus cells, the kinetics of the Hodgkin-Huxley type Na^+ and K^+ channels were modeled in accordance with those in models of stellate cells (Banks and Sachs, 1991) and pyramidal cells (Hewitt and Meddis, 1995) of the dorsal cochlear nucleus. The kinetics of the 4-AP sensitive K^+ channel, K_{LT}, were modified from those of the type II neurons in ventral cochlear nucleus (Manis and Marx, 1991). The kinetics of I_h vary greatly from one neuron type to another (McCormick and Pape, 1990; Banks et al., 1993; Tabata and Ishida, 1996). Although Banks et al. (1993) have reported second-order kinetics for I_h associated with MNTB cells, studies of other cell types revealed first-order kinetics. In our representation, we emphasized their slow dynamics and different time courses of activation and deactivation and chose to use only first-order kinetics. The detailed kinetics of each channel type can be found in the Appendix.

In the axon compartment, only Hodgkin-Huxley type Na^+ and K^+ channels were included, as in the stellate cell model of Banks and Sachs (1991). For the soma, in addition to the Na^+ and K^+ channels, we also included the 4-AP sensitive K^+ channel, K_{LT}, and the Cs^+-sensitive, hyperpolarization-activated inward rectifier I_h, which are known to exist in octopus cells (Golding et al., 1995). The maximum conductances of the soma Na^+ and K^+ channels are much lower than those used in the stellate (chopper) cell model in Banks and Sachs (1991), since the Na^+ and K^+ channels are responsible for generating spikes (Hodgkin and Huxley, 1952b), and it was suggested that the action potentials in octopus cells are generated at the axon stage (Golding et al., 1995).

The dendritic compartments are interconnected with serial resistors (cf. Fig. 1B), the conductance of which, as calculated from the geometric data of the dendritic compartments and the axial resistivity (R_i), is 1.96×10^{-6} S. The conductance between the soma and the first dendritic compartments is twice that of the inter-dendritic compartments, since the soma is considered to have zero electrotonic length. The axon compartment is connected to the soma compartment with a serial resistor, which has a conductance calculated to be 1.3×10^{-7} S.

As shown in Fig. 1C, there are at least two branches in the circuit representation of each compartment: the capacitance branch representing the membrane capacitance (C_m) and the leakage branch (g_{leak}-E_{leak}) representing the leakage channel. In each dendritic compartment, the leakage branch has a conductance of 1.57×10^{-9} S (calculated using the membrane area of the compartment and the membrane resistivity, R_m) and a leakage equilibrium potential, chosen to be equal to the resting membrane potential of -62 mV. The axon and soma compartments contain active channels (represented by g_i-E_i branches in Fig. 1C). Following the usual practice (e.g. Rothman et al., 1993), we fixed the soma leakage conductance (at 3.217×10^{-8} S, a value calculated using the membrane area of the soma and the membrane resistivity, R_m) and adjusted the leakage equilibrium potential (~ -58.4 mV) to maintain a stable resting membrane potential of -62 mV. For the axon compartment, we fixed the leakage equilibrium potential (at -53 mV) instead and adjusted the leakage conductance (~ 2.57×10^{-9} S). The value of the resting potential is somewhat arbitrary, considering the wide range of values reported for octopus cells in the literature (*in vivo*: -10 to -70 mV in Romand,

1978; about -30 mV in Rouiller and Ryugo, 1984; -35 to -70 mV in Feng et al., 1994; in slice: -50 to -70 mV in Golding et al., 1995).

2. The stellate cell model

The stellate (chopper) cell is known to fire regularly to stimulation even at low levels (Oertel, 1983; Oertel et al., 1988; Rhode and Smith, 1986a). It would help us gain insight into the mechanisms of onset responses if the chopper response associated with the stellate cell models could be converted into an onset response by modifying a specific set of model parameters. Thus we implemented a stellate cell model based on that of Banks and Sachs (1991). The morphological and basic electrical parameters were as described in their paper. Specifically, the model cell has a soma 25 μm in diameter, an axon 70 μm in length and 3 μm in diameter, six dendrites each 600 μm in length and 2.2 μm in diameter. The membrane capacitance density (C_m) was 1 $\mu F/cm^2$, the membrane resistivity (R_m) was 10 $k\Omega \cdot cm^2$ and the axial resistivity (R_i) was 150 $\Omega \cdot cm$. The only modification was in relation to the Na^+ and K^+ channel kinetics. We chose the kinetics specified by Hewitt and Meddis (1995) for pyramidal cells of dorsal cochlear nucleus, but made minor adjustments in parameters to produce responses to current inputs that were similar to those reported in Banks and Sachs (1991) [1].

3. The simulation program

Simulations were performed on either a PC under DOS or unix workstations with a program developed in our laboratory (Cai et al., 1997). The program automatically configures the model according to information available in a parameter file, which was used to store model parameters. To simulate different models and/or conditions, the parameter file can be adjusted, and no change in the simulation program is necessary. Notice that all compartments, whether they contain active channels or not, are treated uniformly (cf. Fig. 1C). One differential equation can then be written for each compartment. Due to the uniform treatment of all compartments, these equations have the same form. The conductances of the active channels are treated the same way as fixed conductances in the equations, but the conductance values are updated at each time step according to the kinetics of the channels. The equations were solved numerically using the modified Crank-Nicolson method (Hines, 1984) and a

simple approach for solving equations with branching geometries (Cai et al., 1997). DC currents and halfwave-rectified sinewaves were used as stimuli. The results were obtained at a resolution of 10 μs. However, the data shown in the figures were further sub-sampled at a rate of 1:16. With our model configuration, it takes a few seconds to finish one simulation on a Pentium-130 PC under DOS.

Results

1. The stellate cell model can demonstrate onset responses

As described in Methods, we implemented a stellate cell model based on that of Banks and Sachs (1991) in an effort to generate onset responses by adjusting appropriate model parameters, hoping to gain insight into the mechanisms underlying the production of onset responses. With the original parameters, the model fires regularly in response to depolarizing current (Fig. 2A), even at threshold levels.

It was hypothesized that the Na^+ channel can be opened by three activating particles, each with a probability m of being in the right place, and inactivated with a probability (1-h) when blocked by one inactivating particle (Hodgkin and Huxley, 1952b). Thus, the conductance of the Na^+ channel is proportional to m^3h (cf. equation in the Appendix), and the smaller the value of "h", the more inactivated the Na^+ channel. Shown in Fig. 2B are the changes of "m" and "h" parameters of the Na^+ channel during the action potentials. During each action potential, the "h" parameter changes from a high value (non-inactivated status) to near zero (inactivated status), then back to a high value after each spike occurs.

Electrical parameters of the model were then modified in an effort to change the sustained spike train into one exhibiting onset spikes only. Most modifications only affected the firing rate and/or the morphology of the action potential, but the basic chopper pattern was unaffected. Increasing the leakage conductance (or decreasing the membrane resistivity R_m), however, produced onset responses.

(Fig. 2 about here)

Figure 3 shows the response of the model to a 40-ms depolarizing current injection, when the leakage conductance in the dendrites was increased by a factor of 10. Other parameters were the same as in Fig. 2. As can be seen, the model responded with only one action potential at the onset of the stimulus, followed by a sustained steady-state depolarization. The values of the "h" parameter dropped transiently during the action potential, but rapidly returned to a high level and maintained a slightly decreased value relative to rest during the steady-state. Although it is difficult to determine the exact contribution of depolarization block (the decrease of "h") in the generation of the onset response, it is clear that the larger membrane conductance (contributed by the leakage channel) in the dendrite played a key role in the production of the onset response.

(Fig. 3 about here)

2. Basic onset responses from the octopus cell model

Although onset responses were successfully produced by modifying the stellate cell model, the response was not realistic. For example, the soma spike is large, and the response reverts to regular firing when the stimulus level is increased slightly. Additionally, the morphology of the model cell is different from that of the octopus cell, and the model does not include the ionic channels that are known to exist in octopus cells.

In our octopus cell model, we set the membrane conductivity to be 10 times that of the stellate cell model (the resistivity, or inverse of conductivity, is 1 $k\Omega \cdot cm^2$, or one tenth of that of the stellate cell model, see Methods). Since it has been suggested that in octopus cells action potentials are generated at the axon hillock (Golding et al., 1995), we used relatively low maximum conductances for soma Na^+ and K^+ channels (0.01 nS/cm^2 for both, while the corresponding values in the stellate cell model were 0.17 and 0.04 nS/cm^2, respectively). The responses of the model neuron to current injections at the soma are shown in Figs. 4 and 5. Due to the large membrane area and large resting membrane conductance (including those contributed by I_h and K_{LT}), the current level used was much higher than that used in the stellate model. With low-level DC current injection, the model neuron fired one action

potential at the onset of the stimulus, followed by a steady-state depolarization (Fig. 4). The soma spike is small, reaching only about -25 mV, whereas the axon spike is large. These characteristics are similar to those observed experimentally (Feng et al., 1994; Golding et al., 1995). Notice that although the value of the "h" parameter decreased transiently, it remains at a high sustained level, suggesting that the Na^+ channel was only slightly inactivated. Instead, there was a significant increase in the conductance of K_{LT}.

(Figs. 4 and 5 here)

Due to the rectifying characteristic of the transfer functions of the inner hair cells (e.g. Dallos, 1986; Russell et al., 1986), auditory-nerve fibers fire preferably during half of a stimulus cycle in response to low-frequency stimulation, as evidenced from the phase-locking in the responses of auditory-nerve fibers (e.g. Rose et al., 1967). Thus the use of halfwave-rectified sinewaves as stimuli mimicked, in some aspect, the inputs of the ensemble of auditory-nerve fibers, since octopus cells are thought to converge inputs from many auditory-nerve fibers based on their broad tuning and their high threshold (e.g., Godfrey et al., 1975; Rhode and Smith, 1986a). In Fig. 5, we show the response of the model octopus cell when a 300-Hz, halfwave-rectified sinewave current was used as the stimulus. The model parameters were the same as those used in the DC current simulation in Fig. 4. The result was also similar to that shown in Fig. 4. The model responded with only one action potential at the first stimulus cycle. Subsequent cycles of stimulation only evoked small membrane depolarizations, although the sustained value of the "h" parameter remained at a high level throughout stimulation. The conductance of K_{LT} was, however, increased, as with DC current stimulation in Fig. 4 (but the sustained level of K_{LT} in Fig. 5 was lower than that in Fig. 4, due to the less effective stimulation in the case of the halfwave-rectified sinewave current).

3. Role of the kinetics of the low-threshold K^+ channel, K_{LT}, and the Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h

The results in Figs. 4 and 5 suggested a link between onset response and the rise of the conductance of K_{LT}. In Figs. 6 and 7, we explore in more detail the effects of the kinetics of K_{LT} upon responses of the model. The results shown in Fig. 6 were obtained with the same

model parameters as those that produced the results in Fig. 5. We also used the same stimulus, a 300-Hz, halfwave-rectified sinewave current, except at a higher level. A higher level stimulus evokes more spikes during the stimulation and thus affords us the chance to study the dynamics of the kinetics. As expected from the entrainment of responses of octopus cells to low-frequency acoustic stimulation (e.g., Rhode and Smith, 1986a), the spikes are timed to the depolarization events (and changes in the stimulus) [2].

Examination of the exact response pattern shows that the model responded to the first stimulus cycle with a spike, missed one, fired one spike, then missed two cycles, and so on; i.e., the pattern of missing spikes is 1, 2, 2. Examination of the "h" and "m" parameters (Fig. 6D) indicates that there was no visible difference in the values of the "h" parameter at the instant just prior to the firing of one spike and at the corresponding instant preceding a stimulus cycle (downward arrows) which did not evoke a spike. There was also no difference in the values of the "m" parameter (upward arrows) or in the conductances of Na^+ and K^+ channels (arrows, Fig. 6E-F). However, there was a significant difference in the conductance of K_{LT} (arrows, Fig. 6C), supporting our contention that K_{LT} is a regulatory conductance.

To further establish the role of K_{LT} in the onset response, we tried to "slow" down the kinetics of K_{LT} and examine any possible change in the spike pattern. We used the same stimuli as in Fig. 6, but changed the B_{fac} of the K_{LT} kinetics from 0.75 to 1.0, the effect of which was to proportionally increase the time constant of the "B" parameter at all membrane voltages and thus slow down the kinetics by a factor of 4/3 (cf. the description of K_{LT} kinetics in the Appendix). In the responses shown in Fig. 7, the first two spikes occurred at the same time as did corresponding spikes in Fig. 6, but after the second spike, three depolarizing events were missed before the "cell" fired the third spike, and so on. The missing pattern is now 1, 3, 3 instead of 1, 2, 2. Since the only parameter change involved B_{fac} of the K_{LT} kinetics, the results shown in Figs. 6 and 7 demonstrate that the kinetics of K_{LT} are important in the regulation of the firing pattern of the octopus cell model and further support the idea that K_{LT} contributes to the onset response.

In Fig. 6A, the post-spike pattern of non-spiking depolarizations was 1, 2, 2 during the first 30 ms of the response. We expected the model neuron to fire a fifth spike in the third stimulus

cycle after the fourth spike, at the position indicated by the left-downward arrow. It did not. Examination of the kinetics of various channels implemented in the model indicates that the conductances of all channels at the beginning of the missing spike and at the beginning of the fourth spike are the same, with the exception of I_h. This led us to consider the possibility that "the missing 5th spike" resulted from a decrease in the conductance of I_h. To test this hypothesis, we fixed the conductance of I_h at its resting level and repeated the simulation (Fig. 8). Under these conditions, the fifth spike appeared on the 3rd post-spike depolarization after the 4th spike, as predicted according to the 1, 2, 2 sequence observed during the preceding 30-ms post-stimulus period (Fig. 8A, left-downward arrow).

4. Level of Na^+ channel inactivation is not a major factor

In the example shown in Fig. 9, we implemented a parameter set in which the model neuron fired more than one spike at the onset of a DC stimulus, followed by a sustained depolarization. We then evaluated the status of Na^+ channel inactivation during the spiking events and the steady-state by examining the values of the "h" parameter. Such a firing pattern was achieved by using a higher maximum conductance of I_h (0.02 nS/cm^2 in this case) and higher level currents. Although no intracellular data exist suggesting that an octopus cell can fire multiple spikes at stimulus onset in response to a depolarizing current, this manipulation is nevertheless helpful. Across a relatively wide range of stimulus levels (from less than 1.8 nA to 2.9 nA), the model neuron maintained its single-spike pattern (data not shown), suggesting that the basic model parameter might not be atypical for an octopus cell. When a 3.3-nA current was used, the model neuron fired three spikes (Fig. 9). As can be seen from the figure, the values of the "h" parameter just before the second and third spikes are lower (Na^+ channel more inactivated) than that during the steady-state. This result suggests that the level of Na^+ channel inactivation (or depolarization block) is not a major factor determining the temporal response pattern of octopus cells.

5. Onset response produced with "depolarization block"

Since it has been suggested that onset responses are due to "depolarization block" (Ritz and Brownell, 1982; Feng et al., 1994), we adjusted our model parameters to simulate onset

responses under conditions of "depolarization block" (Fig. 10A). We used the basic octopus cell model, but disabled the low-threshold K^+ channel, K_{LT}, and the Cs^+-sensitive inward rectifier, I_h, and used high-level current to produce the response. In this example, the Na^+ channel was clearly inactivated as evidenced by the small value of "h" during the current injection (Fig. 10B). At low stimulus levels, the model neuron responded with an onset response similar to that shown in Fig. 3. As the stimulus level was slightly increased, the response became regular (not shown). Since a high-level stimulus had to be used to obtain the results shown in Fig. 10, and since we did not implement K_{LT} and I_h, which are known to exist in octopus cells (Golding et al., 1995), the onset response in Fig. 10 is probably not what would happen under physiological conditions.

Discussion

The low input impedance of octopus cells makes it difficult to study their properties *in vivo* (Golding et al., 1995), which probably explains, in part, the lack of experimental data available regarding the characteristics of these cells. Computer modeling allows the opportunity to simulate conditions that are difficult or sometimes impossible to achieve experimentally. In this study, we have used a computer model to investigate possible mechanisms underlying the production of onset responses in octopus cells.

Mechanisms of onset responses in octopus cells

Although early studies focused on the possibility that neurons projecting as interneurons or inhibitory inputs played a central role in the generation of onset responses in octopus cells (See Introduction), our model included neither network nor inhibitory inputs, yet it successfully simulated the onset response. This result supports previous suggestions that the basic onset response pattern does not require the involvement of neuronal circuitry (Kane, 1973; Morest et al., 1973; Godfrey et al., 1975) or inhibitory inputs (Wickesberg et al., 1991) [3]. Although the result does not support the idea that the onset response requires inhibitory inputs, it does not exclude the possibility that inhibitory inputs help to shape other

characteristics of the response. However, results reported here support the view that the onset pattern reflects the intrinsic properties of octopus cells.

The results obtained with the stellate cell model (Figs. 2 and 3) suggest that overall membrane conductance is the key factor shaping the onset response. This agrees with the finding that the input impedance of octopus cells is usually very low (Golding et al., 1995). It should be pointed out that, under the conditions of Figs. 2 and 3 (the stellate cell model), the membrane conductance is formed by the leakage conductance alone. However, as shown in Figs. 4-9 (the octopus cell model), the contribution from different channels can be potentially significant. The membrane conductance may be formed mainly by resting conductances of different channels (probably mainly the Cs^+-sensitive inward rectifier I_h, see Golding et al., 1995).

As we have shown (Figs. 3 and 10), models that only incorporate large leakage conductances do not produce realistic onset responses and can produce a regular firing pattern at higher stimulus levels. Therefore, there must be other important factors involved in the generation and regulation of the onset responses. The results shown in Figs. 4-7 suggest that the low-threshold, 4-AP sensitive K^+ channel, K_{LT}, plays an important role in producing and regulating the onset response pattern in octopus cells. Such a role is consistent with the K_{LT}'s role in the generation of the onset-like response in type II (bushy) neurons of the ventral cochlear nucleus (Manis and Marx, 1991) and in MNTB neurons (Banks and Smith, 1992). The Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h, also plays a role in the production of the transient, onset spike among these cell types. In addition to its contribution to the membrane conductance, I_h regulates the response pattern (Figs. 6 and 8). But due to its slow kinetics, its regulatory role is probably mainly limited to longer term effects under the conditions we used in this study.

In most of our simulations (Figs. 3-9), the value of the "h" parameter was only slightly decreased during "stimulation", although sustained depolarization was evident in every example where the onset response was generated. This suggests that sustained depolarization does not necessarily lead to inactivation of the Na^+ channel (or depolarization block). Furthermore, these results suggest that depolarization block is *not* a major factor in the

generation of onset response in octopus cells, as suggested in earlier postulates (Ritz and Brownell, 1982; Feng et al., 1994). The fact that Na^+ channel inactivation occurred only at high stimulus levels, and that K_{LT} and I_h had to be disabled (Fig. 10), also supports this conclusion.

Model parameters

There is very little information in the literature about the specific kinetics of channels expressed in octopus cells (esp. K_{LT} and I_h). For this reason, it is difficult to identify a set of parameters that fits the fine aspects of most of the existing experimental data. We implemented a wide range of parameters based on existing information regarding the responses of octopus cells, and, although the basic onset responses were routinely produced, the precise response characteristics differ from one set of parameters to another. As shown in Fig. 3, the basic onset response is generated as long as there is a large membrane conductance, and more realistic onset responses (e.g. small soma spikes) can be generated when the soma spike-generating mechanism is minimized (small values of Na^+ and K^+ channel conductances, Figs. 4 and 5). Although the model parameters selected here may not be physiologically accurate, our choice would not affect the general conclusion (i.e., that the onset response is due to intrinsic properties of octopus cells, and the underlying mechanism is determined by a combination of factors, and that depolarization block is not a major factor). Likewise, the possible exclusion of some minor ionic channels currently not yet identified also would not affect the general conclusion. To simulate the actual responses, there is no doubt that modification and fine tuning of model parameters used here will be required. On the other hand, since onset responses can be generated with a wide range of model parameters, this diversity might correspond to the diversity in characteristics of onset responses observed *in vivo* (e.g. Godfrey et al., 1975; Rhode and Smith, 1986a).

We should also point out that, although our choice of parameters will not affect the general conclusion, it will affect discussions about the contributions of specific factors. One such area concerns the I_h conductance. If we set the I_h conductance to a larger value, even given the selection of parameters resulting in slow kinetics, it can play a more important role, and its action may be more consistent with actual physiological conditions. Golding et al. (1995)

have concluded that I_h contributes substantially to the low impedance of octopus cells measured in brain slice. That means that part of the leakage conductance in our model should be replaced with the I_h conductance. Another consideration involves the dendritic model. In our model, we assumed that dendrites are passive and leaky. As noted in the Methods, there is increasingly more evidence suggesting the presence of active dendrites in a variety of cell types. If the dendrites of octopus cells are active (or the proximal stages are active), part of the resting membrane conductance will be formed by the active channels instead of the leakage channel. Accordingly, the regulatory role of the active channels will increase. Only further experimentation will ascertain whether our model assumptions and parameter choices are correct, allowing us to validate the conclusions put forth in this paper.

Implications regarding mechanisms of onset responses in other cell types

As mentioned in the Introduction, there are other cell types in the cochlear nuclei producing onset responses. One such cell type is the multipolar stellate cell, found in the anterior portion of the PVCN. While the octopus cell is associated with PSTH sub-types O_I (no activity after the initial onset spikes) and O_L (with low sustained activities) (Rhode et al., 1983; Rouiller and Ryugo, 1984; Feng et al., 1994; Rhode and Greenburg, 1992), the multipolar cell is associated with the PSTH sub-type O_C, as it displays two to four modes of "chopping" at stimulus onset (Smith and Rhode, 1989; Rhode and Greenburg, 1992; Palmer et al., 1996). This cell type shares many characteristics with the octopus cell, for example, it also has large and relatively unbranched dendrites (Smith and Rhode, 1989; Rhode and Greenburg, 1992), and it is also thought to achieve its temporal precision by integration from a large number of auditory inputs (Palmer et al., 1996), as in the octopus cell (Golding et al., 1995). It is natural to assume that some of the mechanisms operating in octopus cells also play a role(s) in the production of onset responses in multipolar cells. In fact, the responses shown in Fig. 9 are reminiscent of those produced by multipolar cells. Palombi and Caspary (1992) reported that bicuculline alters the post-onset discharges of chichilla PVCN neurons, suggesting that GABAergic inhibitory inputs contribute to their onset responses. However, a more recent study in guinea pigs (Evans and Zhao, 1997) showed that O_C units are sensitive to bicuculline but O_I units (octopus cells) are not. This later result agrees with the finding that there are inhibitory projections to the multipolar cell area but not to the OCA in mice (Wickesberg et

al., 1991). Computer simulations have shown that inhibitory inputs are also important in the production of onset-like responses in bushy cells (Rothman et al., 1993). The bushy cell also contains the low-threshold, 4-AP sensitive K^+ channel (K_{LT}), which is proposed to increase the membrane conductance and contribute to the onset response (Manis and Marx, 1991). Thus, it seems that different cell types share not only the basic onset response pattern, but also similar mechanisms that may produce such response patterns. These seemingly different cell types may simply form a continuum of response patterns. If that is the case, one might expect stellate cells to produce onset responses as a result of a higher membrane leakage conductance (Figs. 2 and 3).

Summary

We have used a computer model to study the mechanisms of onset responses in octopus cells. Our results suggest that the basic onset response pattern does not involve neuronal circuitry or inhibitory inputs, but reflects actions of the intrinsic properties of octopus cells. A large membrane conductance, partly contributed by the Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h, is the key factor. The low-threshold, 4-AP sensitive K^+ channel plays a major role in the regulation of the response pattern, while the role of I_h, due to its slow kinetics, must be limited to a long term regulation under the conditions used in this investigation. Depolarization block, or Na^+ channel inactivation, plays only a minor role, if any. To better determine the relative importance of factors contributing to this aspect of octopus cell function, more experimental data, especially those characterizing the kinetics of different channels, is needed.

Note added-in-proof

Golding et al. (1997) recently showed that octopus cells can have a membrane time constant of ~200 μs. While this will not affect the basic conclusions in this paper, it suggests that the kinetics of the ionic channels in octopus cells might be faster than those used in our simulation.

Text Footnotes

[1] The model failed to produce the proper response patterns reported in Banks and Sachs (1991) when the K^+ channel kinetics as described in their paper were implemented. So we used the kinetics of Hewitt and Meddis (1995), which lack a voltage-dependent term (not critical for the basic response pattern) used in that of Banks and Sachs (1991). The Na^+ channel kinetics in both studies were almost identical.

[2] When the stimulus presentation is repeated (i.e., similar to that during experiments using acoustic stimuli), the spike pattern is not likely to change in consecutive stimulus presentations, and the PSTH so produced would not be realistic. If spike trains from auditory-nerve fibers were used as stimuli, however, the spike pattern in the model output would change in consecutive stimulus presentations (due to the "randomness" in the inputs and synaptic events), producing a more realistic PSTH. Thus, the use of the 300-Hz, halfwave-rectified sinewave current to simulate acoustic stimulation was not useful when a realistic PSTH was the goal. However, it is useful to study the model behavior on one-trial basis, as in our case.

[3] Earlier suggestions that inhibitory inputs shaped the temporal response patterns of octopus cells were based on the presence of thin, presumably inhibitory, auditory-nerve fiber collaterals making direct contacts with octopus cells and did not involve neural circuits (Kane, 1973; Morest et al., 1973; Godfrey et al., 1975). In more recent literature, it is often unclear whether "inhibitory inputs" or "inhibition" also included those mediated by neural circuitry. In our discussion, we chose not to distinguish the two, since our results do not support the role of inhibitory inputs of any kind. Due to the latency constraint (see Introduction), the more synapses the neural circuitry contains, the less likely they are involved in the generation of onset response. Golding et al. (1995) recently suggested that the presumed thin auditory-nerve fiber collaterals described by Kane (1973) might come from octopus cells.

Acknowledgments

This work was supported by the National Institute on Deafness and Other Communication Disorders, US National Institutes of Health, grant number DC01007. Yidao Cai is supported, in part, by research grant number P60 DC00982-06 from the same institute. The authors wish to thank Dr. M. J. Ferragamo and two reviewers for helpful criticisms of the manuscript, and Drs. D. Oertel and W. S. Rhode for helpful discussions.

Appendix

A general description of the parameters determining the channel conductances is given by

$$\tau_p \, dp / dt + p = p_\infty,$$

and

$$\tau_p = P_{fac} / (\alpha_p + \beta_p),$$

$$p_\infty = \alpha_p / (\alpha_p + \beta_p),$$

where τ_p (in ms) is the time constant for parameter "*p*" ($p \subset [0,1]$ and p is a function of both time t and membrane voltage V, in mV), p_∞ is the value of p after the membrane voltage being held at a constant level for infinite time, P_{fac} is the temperature factor for time constant τ_p, and α_p and β_p are rate constants and functions of membrane voltage only. The "*p*" parameter in the above equations is to be replaced by any one of "m", "h", "n", "B" or "i_h" in the descriptions below. For example, to describe the "m" parameter, τ_p becomes τ_m, P_{fac} becomes M_{fac}, and so on.

1. The Na^+ channel conductance is the same as in Hewitt and Meddis (1995) and is described by

$$gNa = gNa_{max} \, m^3 \, h \, S,$$

$$\alpha_m = -0.1 \, (V + 37 + M_{SH}) / (\exp(- (V + 37 + M_{SH}) / 10) - 1),$$

$$\beta_m = 4 \exp(- (V + 62 + M_{SH}) / 18),$$

$$\alpha_h = 0.07 \exp(- (V + 62 + H_{SH}) / 20),$$

$$\beta_h = 1 / (\exp(- (V + 32 + H_{SH}) / 10) + 1),$$

where gNa_{max} is the maximum conductance per unit area (S/cm^2), "m" and "h" are the activation and inactivation parameters respectively, and S is the membrane area of the compartment. The values of gNa_{max}, M_{SH}, H_{SH}, M_{fac} and H_{fac} for the soma are given in the figures. For the axon (of both the stellate cell model and the onset cell model), $gNa_{max} = 0.17$ S/cm^2, $M_{SH} = 2.3$, $H_{SH} = -10.8$, and $M_{fac} = H_{fac} = 0.1315$. The Na^+ equilibrium potential E_{Na} is 55 mV.

2. The K^+ channel conductance is also the same as in Hewitt and Meddis (1995) and is described by

$$gK = gK_{max} \, n^4 \, S,$$

$\alpha_n = -0.01\ (V + 52 + N_{SH}) / (\exp(- (V + 52 + N_{SH}) / 10) - 1)$,

$\beta_n = 0.125 \exp(- (V + 62 + N_{SH}) / 80)$,

where gK_{max} is the maximum conductance per unit area (S/cm^2), and "n" is the activation parameter. The values of gK_{max}, N_{SH} and N_{fac} for the soma are given in the figures. For the axon (of both the stellate cell model and the octopus cell model), $gK_{max} = 0.02\ S/cm^2$, $N_{SH} = 2.65$ and $N_{fac} = 0.6575$. The K^+ equilibrium potential E_K is -80 mV.

3. The kinetics of the low-threshold, 4-AP sensitive K^+ channel, K_{LT}, are modified from Manis and Marx (1991),

$gK_{LT} = gK_{LTmax}\ B\ S$,

$\alpha_B = \alpha_B 0 \exp((V - V_{1/2} - B_{SF}) / K_\alpha)$,

$\beta_B = \beta_B 0 \exp(- (V - V_{1/2} - B_{SF}) / K_\beta)$,

where $V_{1/2}$ (= -53 mV) is the half activation voltage. The values of gK_{LTmax} and other parameters are given in the figures. The equilibrium potential E_{KLT} is -77 mV. In the original description of Manis and Marx (1991), the minus sign in the exp() function of β_B was misplaced in that of α_B. We also changed the form of expression so that it resembles those of the Na^+ and K^+ channels.

4. The kinetics of the Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h, were based on the data of McCormick and Pape (1990) and Banks et al. (1993). We did not use the activation and deactivation rate constants (as used for other channel types), although such treatment was also used for I_h (Tabata and Ishida, 1996). The description is as follows,

$gI_h = gI_{hmax}\ i_h\ S$,

$\tau_{ih} = (110 + V)^2 + 50$, for activation process,

$\tau_{ih} = -1000\ (5.75 + 0.11\ V) / 3$, for deactivation process,

$i_{h\infty} = 1 / (1 + \exp((V - V_{1/2} - IH_{SF}) / K_S))$,

where $\tau_{ih} \subset [50, \infty)$ and $V_{1/2}$ (= -75 mV) is the half activation voltage. The equilibrium potential E_{Ih} is -45 mV.

Reference

Adams, J. C. and Mugnaini, E. Patterns of glutamate decarboxylase immunostaining in the feline cochlear nuclear complex studied with silver enhancement and electron microscopy. *J. Comp. Neurol.* 262: 375-401, 1987.

Adams, J. C. and Warr, W. B. Origins of axons in the cat's acoustical striae determined by injection of horseradish peroxidase into severed tracts. *J. Comp. Neurol.* 170: 107-122, 1976.

Altschuler, R. A., Betz, H., Parakkal, M. H., Reeks, K. A., and Wenthold, R. J. Identification of glycinergic synapses in the cochlear nucleus through immunocytochemical localization of postsynaptic receptors. *Brain Res.* 369: 316-320, 1986.

Banks, M. I. and Sachs, M. B. Regularity analysis in a compartmental model of chopper units in the anteroventral cochlear nucleus. *J. Neurophysiol.* 65: 606-629, 1991.

Banks, M. I. and Smith, P. H. Intracellular recordings from neurobiotin-labeled cells in brain slices of the rat medial nucleus of the trapeziod body. *J. Neurosci.* 12: 2819-2837, 1992.

Banks, M. I., Pearce, R. A., and Smith, P. H. Hyperpolarization-activated cation current (I_h) in neurons of the medial nucleus of the trapeziod body: Voltage-clamp analysis and enhancement by norepinephrine and cAMP suggest a modulatory mechanism in the auditory brain stem. *J. Neurophysiol.* 70: 1420-1432, 1993.

Bawer, J. B., Morest, D. K., and Kane, E. C. The neuronal architecture of the cochlear nucleus of the cat. *J. Comp. Neurol.* 155: 251-300, 1974.

Cai, Y., Walsh, E. J., and McGee, J. A simple approach for simulating responses of neurons with arbitrarily structured dendritic trees. *J. Neurosci. Methods* (in press), 1997.

Dallos, P. Neurobiology of cochlear inner and outer hair cells: intracellular recordings. *Hear. Res.* 22: 185-198, 1986.

DiFrancesco, D. A study of the ionic nature of the pace-maker current in calf Purkinje fibres. *J. Physiol.* 314: 377-393, 1981.

Evans, E. F. and Zhao, W. Onset units in guinea pig ventral cochlear nucleus: Neuropharmacological studies. *Assoc. Res. Otolaryngol. Abstr.* 20: 116, 1997.

Feng, J. J., Kuwada, S., Ostapoff, E.-M., Batra, R., and Morest, D. K. A physiological and structural study of neuron types in the cochlear nucleus. I. Intracellular responses to acoustic stimulation and current injection. *J. Comp. Neurol.* 346: 1-18, 1994.

Friauf, E. and Ostward, J. Divergent projections of physiologically characterized rat ventral cochlear nucleus neurons as shown by intra-axonal injection of horseradish peroxidase. *Exp. Brain Res.* 73: 263-284, 1988.

Godfrey, D. A., Kiang, N. Y. S., and Norris, B. E. Single unit activity in the posteroventral cochlear nucleus of the cat. *J. Comp. Neurol.* 162: 247-268, 1975.

Golding, N. L., Robertson, D., and Oertel, D. Recordings from slices indicate that octopus cells of the cochlear nucleus detect coincident firing of auditory nerve fibers with temporal precision. *J. Neurosci.* 15: 3138-3153, 1995.

Golding, N. L., Ferragamo, M. J., and Oertel, D. Octopus cells: Fastest cells in the brain? *Assoc. Res. Otolaryngol. Abstr.* 20: 116, 1997.

Hewitt, M. J. and Meddis, R. A computer model of dorsal cochlear nucleus pyramidal cells. *J. Acoust. Soc. Am.* 97: 2405-2413, 1995.

Hines, M. Efficient computation of branched nerve equations. *Int. J. Biomed. Comput.* 15: 69-76, 1984.

Hirsch, J. A. and Oertel, D. Intrinsic properties of neurons in the dorsal cochlear nucleus of mice, *in vitro*. *J. Physiol.* 396: 535-548, 1988.

Hodgkin, A. L. and Huxley, A. F. The dual effect of membrane potential on sodium conductance in the giant axon of *loligo*. *J. Physiol.* 116: 497-506, 1952a.

Hodgkin, A. L. and Huxley, A. F. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117: 500-544, 1952b.

Jack, J. J. B., Noble, D., and Tsien, R. W. *Electric Current Flow in Excitable Cells.* Oxford: Oxford University Press, 1983, Chapts. 2 and 3.

Kane, E. C. Octopus cells in the cochlear nuclei of the cat: heterotypic synapses upon homeotypic neurons. *Int. J. Neurosci.* 5: 251-279, 1973.

Kane, E. C. Synaptic organizations in the dorsal cochlear nuclei of the cat: a light- and electron-microscopic study. *J. Comp. Neurol.* 155: 301-330, 1974.

Kiang, N. Y. S., Morest, D. K., Godfrey, D. A., Guinan, J. J. Jr., and Kane, E. C. Stimulus coding at caudal levels of the cat's auditory nervous system: I. Response characteristics of single units. In: *Basic Mechanisms in Hearing,* edited by A. R. Moller. New York: Academic, 1973, p. 455-478.

Lipowsky, R., Gillessen, T., and Alzheimer, C. Dendritic Na^+ channels amplify EPSPs in hippocampal CA1 pyramidal cells. *J. Neurophysiol.* 76: 2181-2191, 1996.

Manis, P. B. and Marx, S. O. Outward currents in isolated ventral cochlear nucleus neurons. *J. Neurosci.* 11: 2865-2880, 1991.

McCormick, D. A. and Pape, H-C. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurons. *J. Physiol.* 431: 291-318, 1990.

Morest, D. K., Kiang, N. Y. S., Kane, E. C., Guinan, J. J. Jr., and Godfrey, D. A. Stimulus coding at caudal levels of the cat's auditory nervous system: II. Patterns of synaptic

organization. In: *Basic Mechanisms in Hearing,* edited by A. R. Moller. New York: Academic, 1973, p. 479-509.

Oertel, D. Synaptic responses and electrical properties of cells in brain slices of the mouse anteroventral cochlear nucleus. *J. Neurosci.* 3: 2043-2053, 1983.

Oertel, D. The role of intrinsic neuronal properties in the encoding of auditory information in the cochlear nuclei. *Current Opinion Neurobiol.* 1: 221-228, 1991.

Oertel, D., Wu, S. H., Garb, M. W., and Dizack, C. Morphology and physiology of cells in slice preparations of the posteroventral cochlear nucleus of mice. *J. Comp. Neurol.* 295: 136-154, 1990.

Oertel, D., Wu, S. H., and Hirsch, J. A. Electrical characteristics of cells and neuronal circuitry in the cochlear nuclei studied with intracellular recordings from brain slices. In: *Auditory Function: Neurobiological Basis of Hearing*, edited by G. M. Edelman, W. E. Gall and W. M. Cowan. New York: John Wiley & Sons, 1988, p. 313-336.

Osen, K. K. Cytoarchitecture of the cochlear nuclei in the cat. *J. Comp. Neurol.* 136: 453-483, 1969.

Ostapoff, E-M., Feng, J. J., and Morest, D. K. A physiological and structural study of neuron types in the cochlear nucleus. I. Neuron types and their structural correlation with response properties. *J. Comp. Neurol.* 346: 19-42, 1994.

Palmer A. R., Jiang, D., and Marshall, D. H. Responses of ventral cochlear nucleus onset and chopper units as a function of signal bandwidth. *J. Neurophysiol.* 75: 780-794, 1996.

Palombi, P. S. and Caspary, D. M. $GABA_A$ receptor antagonist bicuculline alters response properties of posteroventral cochlear nucleus neurons. *J. Neurophysiol.* 67: 738-745, 1992.

Rhode, W. S. Interspike intervals as a correlate of periodicity pitch in cat cochlear nucleus. *J. Acoust. Soc. Am.* 97: 2414-2429, 1995.

Rhode, W. S. and Greenburg, S. Physiology of the cochlear nuclei. In: *The Mammalian Auditory Pathway: Neurophysiology*, edited by A. N. Popper and R. R. Ray. New York: Springer-Verlag, 1992, p. 94-152.

Rhode, W. S., Oertel, D., and Smith, P. H. Physiological response properties of cells labeled intracellularly with horseradish peroxidase in cat ventral cochlear nucleus. *J. Comp. Neurol.* 213: 448-463, 1983.

Rhode, W. S. and Smith, P. H. Encoding timing and intensity in the ventral cochlear nucleus of the cat. *J. Neurophysiol.* 56: 261-286, 1986a.

Rhode, W. S. and Smith, P. H. Physiological studies on neurons in the dorsal cochlear nucleus of cat. *J. Neurophysiol.* 56: 287-307, 1986b.

Ritz, L. A. and Brownell, W. E. Single unit analysis of the posteroventral cochlear nucleus of the decerebrate cat. *Neurosci.* 7: 1995-2010, 1982.

Romand, R. Survey of intracellular recording in the cochlear nucleus of the cat. *Brain Res.* 148: 43-65, 1978.

Rose, J. E., Brugge, J. F., Anderson, D. J., and Hind, J. E. Phase-locked response to low-frequency tones in single auditory nerve fibers of the squirrel monkey. *J. Neurophysiol.* 30: 769-793, 1967.

Rothman, J. S. Young, E. D., and Manis, P. B. Convergence of auditory nerve fibers onto bushy cells in the ventral cochlear nucleus: Implications of a computational model. *J. Neurophysiol.* 70: 2562-2583, 1993.

Rouiller, E. M. and Ryugo, D. K. Intracellular marking of physiologically characterized cells in the ventral cochlear nucleus of the cat. *J. Comp. Neurol.* 225: 167-186, 1984.

Russell, I. J., Cody, A. R., and Richardson, G. P. The responses of inner and outer hair cells in the basal turn of the guinea-pig cochlea and in the mouse grown in vitro. *Hear. Res.* 22: 199-216, 1986.

Saint Marie, R. L., Morest, D. K., and Brandon, C. J. The form and distribution of GABAergic synapses on the principal cell types of the ventral cochlear nucleus of the cat. *Hear. Res.* 42: 97-112, 1989.

Saint Marie, R. L., Benson, C. G., Ostapoff, E.-M., and Morest, D. K. Glycine immunoreactive projections from the dorsal to the anteroventral cochlear nucleus. *Hear. Res.* 51: 11-28, 1991.

Schwartz, A. M. and Kane, E. S. Development of the octopus cell area in the cat ventral cochlear nucleus. *Am. J. Anat.* 148: 1-18, 1977.

Smith, P. H., Joris, P. X., Banks, M. I., and Yin, T. C. T. Responses of cochlear nucleus cells and projections of their axons. In: *The Mammalian Cochlear Nuclei: Organization and Function*, edited by M. A. Merchan, J. M. Juiz, D. A. Godfrey and E. Mugnaini. New York: Plenum Press, 1993, p. 349-360.

Smith, P. H. and Rhode, W. S. Structural and functional properties distinguish two types of multipolar cells in the ventral cochlear nucleus. *J. Comp. Neurol.* 282: 595-616, 1989.

Tabata, T. and Ishida, A. T. Transient and sustained depolarization of retinal ganglion cells by I_h. *J. Neurophysiol.* 75: 1932-1943, 1996.

Warr, W. B. Fiber degeneration following lesions in the posteroventral cochlear nucleus of the cat. *Exp. Neurol.* 23: 140-155, 1969.

Warr, W. B. Fiber degeneration following lesions in the multipolar and globular cell areas in the ventral cochlear nucleus of the cat. *Brain Res.* 40: 247-270, 1972.

Warr, W. B. Parallel ascending pathways from the cochlear nucleus: neuroanatomical evidence of functional specialization. In: *Contributions to Sensory Physiology, Vol. 7*, edited by W. D. Neff. New York: Academic, 1982, p. 1-38.

Wenthold, R. J. Evidence for a glycinergic pathway connecting the two cochlear nuclei: an immunocytochemical and retrograde transport study. *Brain Res.* 415: 183-187, 1987.

Wenthold, R. J., Altschuler, R. A., and Reeks, K. A. Glycine immunoreactivity localized in the cochlear nucleus and superior olivary complex. *Neurosci.* 22: 897-912, 1987.

Wenthold, R. J., Parakkal, M. H., Oberdorfer, M. D., and Altschuler, R. A. Glycine receptor immunoreactivity in the cochlear nucleus of guinea pig. *J. Comp. Neurol.* 276-423-435, 1988.

Wenthold, R. J., Zempel, J. M., Parakkal, M. H., Reeks, K. A., and Altschuler, R. A. Immunocytochemical localization of GABA in the cochlear nucleus of guinea pig. *Brain Res.* 380: 7-18, 1986.

Wickesberg, R. E., Whitlon, D., and Oertel, D. Tuberculoventral neurons project to the multipolar cell area but not to the octopus cell area of the posteroventral cochlear nucleus. *J. Comp. Neurol.* 313: 457-468, 1991.

Wilson, C. J. Dynamic modification of dendritic cable properties and synaptic transmission by voltage-gated potassium channels. *J. Comput. Neurosci.* 2: 91-115, 1995.

Wu, S. H. and Oertel, D. Inhibitory circuitry in the ventral cochlear nucleus is probably mediated by glycine. *J. Neurosci.* 6: 2691-2706, 1986.

Figure Legends

Fig. 1 A. A schematic representation of the octopus cell model (d: diameter; l: length). B. Compartmental representation of the model. The soma and axon are each represented by one compartment (box in the figure), while each dendrite is divided into 20 sections of equal length and thus represented by the same number of compartments. The compartments are interconnected with resistors. C. Details inside each box (compartment). Each compartment contains a membrane capacitor (c_m), and a leakage branch consisting of a resistor (conductance g_{leak}) and a battery (leakage equilibrium potential E_{leak}). It may also contain other branches (g_i-E_i) representing active channels (e.g. Na^+ and K^+ channels).

Fig. 2 The response from a stellate (chopper) cell model, modified from that of Banks and Sachs (1991) (See Methods). A. Membrane voltage of the soma. B. Changes of "m" (dashed line) and "h" (solid line) parameters of the soma Na^+ channel. The model parameters shown on top of the figure are for the soma compartment except otherwise noted, and the injected current into the soma is shown schematically below the voltage response. This convention holds for all other figures in this paper. Abbreviations used in this and other figures: Vm, membrane voltage; Iinj, injected current; freq, stimulus frequency; leakage, soma leakage channel; gNa, gK, gK_{LT}, gI_h, conductances of Na^+, K^+, K_{LT} and I_h respectively; gmax, maximum channel conductance. Refer to the descriptions of channel kinetics in the Appendix for meanings of Msh, Hsh, etc.

Fig. 3 The stellate cell model that produced the responses in Fig. 2 was modified to give rise to an onset response; i.e., the membrane leakage conductance of the dendrites was increased by a factor of 10. A. Membrane voltage of the soma. The same 0.15-nA DC current (threshold level) as in Fig. 2 was used as the stimulus. B. Changes of "m" and "h" parameters of the soma Na^+ channel. Note that the Na^+ channel is not inactivated ("h" parameter remains high).

Fig. 4 The responses of the octopus cell model to a 1.8-nA (slightly above threshold) current injection into the soma. In this and subsequent figures, the results were obtained with the octopus cell model. The model parameters that produced the responses in this figure are

considered to be the reference for those of subsequent figures. A. Membrane voltages of the soma (low amplitude, thick line, arrow) and the axon (high amplitude, thin line, arrow). B. Changes of "m" and "h" parameters of the soma Na^+ channel. C. Change in conductance of the low-threshold, 4-AP sensitive K^+ channel (K_{LT}).

Fig. 5 The responses of the octopus cell model to a 300-Hz, halfwave rectified sinewave stimulus. The peak amplitude was 1.9 nA and the current was injected into the soma. The model parameters were the same as those in Fig. 4. A. Membrane voltages of the soma (low amplitude, thick line) and the axon (high amplitude, think line). Below the voltage responses is the schematic waveform of the stimulus. B. Changes of "m" and "h" parameters of the soma Na^+ channel. C. Change in conductance of the low-threshold, 4-AP sensitive K^+ channel (K_{LT}).

Fig. 6 The responses of the octopus cell model to a 300-Hz, halfwave rectified sinewave stimulus. The peak amplitude of the current was 2.21 nA. The model parameters were the same as those in Figs. 4 and 5. A. Membrane voltages of the soma (low amplitude, thick line) and the axon (high amplitude, thin line). B. and C. Changes in conductances of the Cs^+-sensitive, hyperpolarization-activated inward rectifier (I_h) and of the low-threshold, 4-AP sensitive K^+ channel (K_{LT}). D. Changes of "m" and "h" parameters of the soma Na^+ channel. E. and F. Changes in conductances of Na^+ and K^+ channels. Note that gNa, gK, gK_{LT}, gI_h are conductances of Na^+, K^+, K_{LT} and I_h respectively. See text for details about the arrows.

Fig. 7 The responses of the octopus cell model. The model parameters were the same as those in Fig. 6, except for the B_{fac} of the K_{LT} channel, which was changed from 0.75 to 1.0, a modification that "slowed" the kinetics of the channel by a factor of 4/3. The same 2.21-nA, 300-Hz halfwave rectified sinewave stimulus was used. The format of the figures is the same as in Fig. 6.

Fig. 8 The responses of the octopus cell model. The model parameters were the same as those in Fig. 6, except that the conductance of the Cs^+-sensitive, hyperpolarization-activated inward rectifier, I_h, was fixed at its resting value (B) throughout the simulation. The same 2.21-nA, 300-Hz halfwave rectified sinewave stimulus was used. The membrane voltage

changes of both the soma (low amplitude, thick line) and the axon (high amplitude, thin line) are shown (A).

Fig. 9 The responses of the octopus cell model to a 3.3-nA DC current injection into the soma. The model parameters were the same as those in Figs. 4-6, except that the maximum conductance of I_h was doubled (now 0.02 nS/cm^2). A. Membrane voltages of the soma (low amplitude, thick line) and the axon (high amplitude, thin line). B. Changes of "m" and "h" parameters of the soma Na^+ channel. Notice that the level of the "h" parameter in the steady-state is actually higher (indicating that Na^+ channel less inactivated) than those before the second and third spikes were fired.

Fig. 10 An example of an onset response with Na^+ channels inactivated ("h" low). The basic model parameters were the same as those in Figs. 4-6, but K_{LT} and I_h were disabled. A high level (7 nA DC) stimulus was used. A. Membrane voltage of the soma. B. Changes of "m" and "h" parameters of the soma Na^+ channel. Notice that the level of the "h" parameter is low during the steady-state, indicating that the Na^+ channel was inactivated.