Simulating the Effects of “M-current” Potassium Channels in Cochlear Implant Excitation of Auditory Nerve Fibers

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Abstract
Having an accurate description of the patterns of action potentials (APs) generated in auditory nerve fibers (ANFs) by cochlear implant (CI) stimulation is a crucial component to relating stimulation strategies to perceptual outcomes. Biophysical computational models of ANF are a powerful tool for capturing what is known about the electrophysiological dynamics and ion-channel gating mechanisms underlying neural excitability. Previous computational models of an ANF node of Ranvier suggest that low-threshold potassium (KLT) and hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels affect ANF’s absolute and relative refractory periods and produce adaptation/accommodation to high-rate pulse trains (Boulet and Bruce, 2017; Negm and Yi, 2014). In this study we explore the effects of another type of potassium channel that has recently been identified to be associated with refractory periods and produce adaptation/accommodation to high-rate pulse trains (Boulet and Bruce, 2017; Negm and Yi, 2014). Like the HLT and HCN channels, the M-current is active at the resting membrane potential of ANFs and has slower opening/closing dynamics than the AP-generating sodium and potassium channels. Thus, the M-current is expected to also have an influence over the refractory, facilitation, accommodation and adaptation behavior of ANFs. We have incorporated an M-current model used in other cell types (Lawrence et al., 2006) into the previous ANF model of Boulet and Bruce (2017). As a result of this new model, we have compared simulation results to the room-temperature ANF patch-clamp data of Rutherford et al., (2012). This new model incorporating the M-current is able to better predict these patch-clamp data in general. Further refinement of free parameters in the model is ongoing.

I. INTRODUCTION

As illustrated in Fig. 1, ANFs have a diversity of voltage-gated ion channels that have specific locations and densities along the length of the fiber (Hossain et al., 2005; Kim and Rutherford, 2016; Yi et al., 2010).

II. MODEL STRUCTURE

As shown in Fig. 3, the model used in this study is a stochastic version of the Hodgkin-Huxley (HH) parallel conductance formulation for the action of voltage-gated ion channels on a patch of neural membrane. The previous ANF model of Boulet and Bruce (2017) incorporated HCN & KLT channels in addition to the standard HH model Na ions and K ions. In the proposed model, we include an M-current model used in other cell types (Lawrence et al., 2006). For consistency with the previous model, the Na_{1.1} and K_{1.1} channels and the K_{2.2} and K_{3.1} channels from Fig. 1 are each lumped together into Na_{1} and K_{1} channels modified from the HH model. The potassium channel in the model describes the properties of the K_{1.1} and other low-threshold potassium channels in ANFs.

III. RESULTS

Figure 5 shows example ANF responses of Cells 2010-09-21 & 2010-10-05 to hyperpolarizing and depolarizing current steps along with predictions for different model variants.

IV. DISCUSSION AND CONCLUSIONS

Overall, the model with KLT & HCN channels and 100 M-current channels appears to best predict the example data. For step stimuli, the HCN(q,s)+KLT+M(100) model best describes:
1. the current amplitude at which spiking begins,
2. the sag in hyperpolarization,
3. the magnitude of the summed depolarization following an onset spike, and
4. the occurrence of hyperpolarization-rebound spikes for Cell 2010-10-05.
For ramp stimuli, the HCN(q,s)+M+KLT-M(100) model best describes:
1. the ramp duration at which spiking begins (6 ms), and
2. the jitter in spike latencies.

None of the model variants predict the failure to spike in response to the 20 ms ramp stimulus. However, the HCN(q,s)+KLT+M1000 model does have a much longer spike latency in response to the 20 ms ramp compared to the other model variants, indicating that it may be close to spike failure. Further exploration of M-current model parameters may be warranted.

Alternatively, improved Na_{1} and K_{1} models based on the actual channels identified in mammalian ANFs (see Fig. 1) may be required to explain spike failure for long ramps and the small second spikes that are sometimes observed in onset responses to step stimuli (see Fig. 2A).

REFERENCES