Role of hyperpolarization-activated conductances in the auditory brainstem

Krisztina Szalisznyó

László Zalányi

Department of Biophysics

KFKI Research Institute for Particle and Nuclear Physics of the

Hungarian Academy of Sciences H-1525 P.O. Box 49,

Budapest, Hungary

Abstract

This study examines the possible functional role of two hyperpolarization-activated conductances in the interaural intensity difference detector lateral superior olive (LSO). Inputs of these neurons are transformed into an output, which provides a firing-rate code for a certain interaural intensity difference range. The I_h conductance's effect is partly masked by the inwardly rectifying outward K^+ current's effect. Since resting potential, input resistance, membrane time constant, as well as synaptic release probability are all affected by the pharmacological agents used in vitro experiments, it is not easy to dissect out the role of these conductances. We therefore used computer simulations to investigate this issue. The interplay between the two hyperpolarization activated conductances, first-spike latency, f-I function, input resistance and the width of the dynamic firing regime were examined .

Keywords: Hyperpolarization-activated currents; LSO; Rate code; Width of dynamic regime;

1 Introduction

The lateral superior olive (LSO) is the first nucleus in the ascending auditory pathway that is specialized for interaural sound-intensity difference (IID) detection. LSO is tonotopically organized and azimuthal location is encoded by the position along the isofrequency LSO column, where LSO cell firing first goes to zero. IID detection involves detecting differences in the amplitude and relative timing of synaptic inputs at stimulus onset. The frequency as well as the onset response (for lower frequencies and for moving sound sources) during both depolarization and hyperpolarization is likely to be important. Two hyperpolarization activated conductances were reported recently in these neurons [1]. One is the slowly activating I_h, the other is the very fast inwardly

rectifying outward K^+ conductance. Here we demonstrate and characterize further the possible functional significance of the interplay between these currents in the rate-coding IID detector neurons.

2 Model

We constructed a simple point neuron to investigate the effect of the two hyperpolarization activated conductances. We used the formulations for the point neuron found in Cclamp of Huguenard and McCormick (1994), based on their previous data [2]. We used the two hyperpolarization activated and two spike generating active conductances, and a leak current. Due to the lack of the description of channel kinetics in the literature for these active conductances from the LSO chopper neurons, we used kinetics from a thalamic neuron for the I_h channel. [2]. For the inwardly rectifying conductance, we used channel description from the study by Wessel at al. [3]. This channel is assumed to be voltage dependent, but not time dependent, since it acts quickly, the authors assumed the time dependence to be negligible. The model of the voltage-dependent sodium and potassium channels is borrowed from Connor at all [6]. A voltage-dependent scaling factor on the potassium channel activation time constant is borrowed from Shapiro and Lenherr, in order to adjust the maximum value of the firing rate [4]. Simulations were performed on SUN Ultra-4 station, running Linux operating system, and using XPP simulation software. The differential equations were solved with a 4th order Runge-Kutta method, with a step size 0.05 msec. For the bifurcation analysis the the AUTO part of XPP was used. The current balance equation is given by:

$$C\frac{dV}{dt} = -G_{Na}(V - E_{Na}) - G_K(V - E_K) - G_h(V - E_h) - G_{inw}(V - E_K) - I_{leak} + I_{inj} \quad (1)$$

Where $G_{Na}, G_K, G_h, G_{inw}$ are sodium, potassium, Ih and inwardly rectifying conductances, respectively, V is a membrane potential in millivolts, C is total capacitance. The gating variables are described for sodium, potassium and Ih conductances by the Hodgkin-Huxley formalism:

$$\frac{dx}{dt} = \alpha_x(1-x) - \beta_x x \tag{2}$$

Where x is m,n,h,p gating variables.

$$G_{Na} = \overline{g_{Na}} m^3 h \tag{3}$$

$$G_k = \overline{g_K} n^4 \tag{4}$$

$$G_h = \overline{g_h} p \tag{5}$$

$$I_{leak} = \overline{g_{leak}}(V - E_{leak}) \tag{6}$$

The detailed descriptions for α-s, and β-s are not given here. The inwardly rectifier K^+ current is supposed to act quickly, thus its time dependency is neglected [3].

$$G_{inw} = \overline{g_{inw}} \frac{1}{1 + exp((V - V_{1/2})/\gamma)} \tag{7}$$

The following parameters are used: $C_m = 290pF$, $E_h = -43mV$, $E_K = -80mV$, $E_{Na} = 45mV$, $g_{leak} = 7nS$, $g_{Na} = 60nS$, $g_K = 20nS$, $V_{1/2} = -65mV$, $\gamma = 6$.

3 Results

With this point neuron model we examined questions, that can not be addressed experimentally. The dynamic interplay between the two hyperpolarization activated conductances defines the first spike latency, the resting membrane potential, the input resistance and the duration of the spiking regime. Our model is a Type-I

membrane, where the periodic stable solution emerges via saddle-node bifurcation (as injecting input bias current), with arbitrarily low frequencies [7]. The qualitative analysis of the special points in two dimensions (injected current and the conductances of the two currents) shows, that the width and the location of spiking regime is defined by the two conductances. The I_h conductance-increase moves the saddle node bifurcation point to the left, making the membrane more excitable (fig.3. top figure). The Hopf bifurcation (where the periodic solution vanishes) is not influenced by the I_h total conductance. This is due to the I_h deactivation. The inwardly rectifying conductance moves the saddle node bifurcation to the right, and makes the spiking regime narrower (fig.3. bottom figure). It also moves the Hopf bifurcation (where the periodic solution vanishes) to the right. This bifurcation changes qualitatively, from supercritical to subcritical as a function of the value of the inwardly rectifying conductance. Since these cells are regarded to be rate coders, we examined their frequency responses. On adding the I_h conductance (fig 2.D), the first spike latency decreased, the firing rate curve is shifted to the left at lower frequencies. At higher frequencies, due to the I_h deactivation, the shift decreases, and finally vanishes. (fig.2. C,D). The ratio between the two conductances determines, whether the frequency curve is shifted to the left, or to the right. If only inwardly rectifying conductance is added, due to the nonmonotonicity of the I-V relationship mediated by this conductance, hysteresis can occur, and the Hopf bifurcation (where the periodic solution vanishes) changes qualitatively (from super critical to subcritical). (fig.1). The first spike latency increased, the firing rate curve is shifted to the right to higher currents. (fig.2. A,B).

4 Discussion

Accuracy of rate coding could be "hard wired" by setting the two hyperpolarization activated conductances during development along isofrequency LSO lines, thus neurons with differently expressed hyperpolarization activated conductances could be serially arranged according to threshold [5]. Consistent with the result of Adam at al, the spike count versus prepulse voltage function is nonmonotonic, meaning that if the cell membrane potential is held at different potential levels for a while, and then depolarizing current is applied, the maximum spike number is achieved with prepulse potentials between -60 - 40 mV region [1]. The excitability is decreased in both directions. The inwardly rectifying conductance could contribute to this phenomenon by causing nonmonotonicity in the I-V relationship and also causing voltage dependent nonmonotonous membrane time constant change.

5 Conclusion

We demonstrated, that activation of the I_h conductance by hyperpolarization causes depolarized RMP, and shortens the first spike latency. Though the input resistance decreases and the slope of the I-V curve is shallower, due to the depolarization the cell gets closer to threshold. Inwardly rectifying current partly masks the Ih channel's effect to hyperpolarizing direction, by clamping the cell to the equilibrium potential of potassium, and by decreasing the input resistance further. This K^+ current hyperpolarizes the RMP, induces an increase in the first spike latency, the spike threshold is reached later and decreases the input resistance. Size of synaptic events can be boosted by I_{inw} and decreased by I_h [8], [9]. Both the duration of the firing regime, and the position of the IID/firing regime is affected by the two hyperpolarization activated conductances.

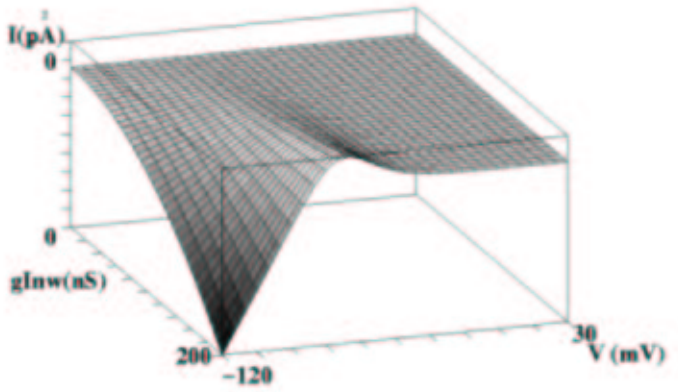


Figure 1:

6 Figure legends

6.1 1. figure legend

Nonmonotonous I-V relationship mediated by the inwardly rectifying conductance. The I-V relationship is examined as a function of the total conductance of the inwardly rectifying current.

6.2 2. figure legend

Bifurcation analysis of our point neuron model, the bifurcation parameter is the injected current. Dots and thick lines are stable periodic solutions and stable fix points respectively, and thin line and empty dots are to denote unstable solutions. Figure A is a bifurcation analysis, where we changed the I_{inw} conductance (with 3 different conductance values). Fig B is the frequency information of the periodic solutions in the same study. Dots denote the frequency values of the stable periodic solutions, empty dots are for the frequency values of the unstable periodec solution. Fig C and D are similar studies, here we changed the conductane of the I_h current

(with 3 different conductance values).

6.3 3. figure legend

Qualitative analysis on the change of special points in two dimensional parameter space. On the top figure we examined the special points in the I_h total conductance-injected current two dimensional space. At the bottom I_{inw} conductance-injected current space was examined.

7 Acknowledgements

We thank to Dan Sanes and Vibhakar Kotak for useful discussions. Part of this work was done at New York University. This work was supported by the national hungarian grant OTKA T038140.

References

[1] **T.G. Adam, P.G. Finlayson, and D.W.F. Schwarz** Membrane properties of principal neurons of lateral superior olive. J Neurophysiol 86 (2001) 922-34.

[2] **D.A. McCormick and J.R. Huguenard** A model of the electrophysiological properties of thalamocortical relay neurons. J Neurophysiol 68 (1992) 1384-400.

[3] **R. Wessel, W.B. Kristan, and D. Kleinfeld** Supralinear summation of synaptic inputs by an invertebrate neuron: dendritic gain is mediated by an "inward rectifier" K(+) current. J Neurosci 19 (1999) 5875-88.

[4] **B.I. Shapiro and F.K. Lenherr** Hodgkin-Huxley axon. Increased modulation and linearity of response to constant current stimulus. Biophys J 12 (1972) 1145-58.

[5] **M.C. Reed and J.J. Blum** A model for the computation and encoding of azimuthal information by the lateral superior olive. J Acoust Soc Am 88 (1990) 1442-53.

[6] **M.I. Banks and M.B. Sachs** Regularity analysis in a compartmental model of chopper units in the anteroventral cochlear nucleus. J Neurophysiol 65 (1991) 606-29.

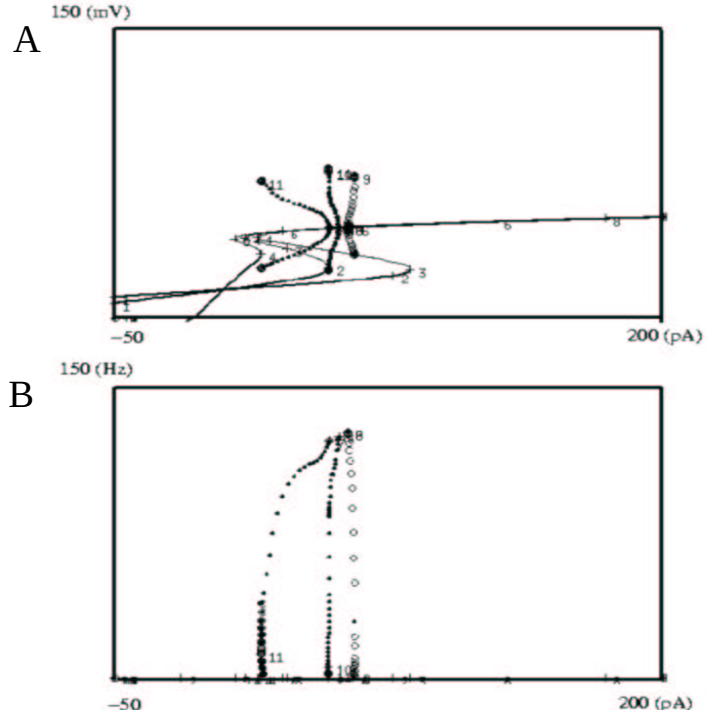
[7] **E.M. Izhikevich** Neural excitability, spiking and bursting International Journal of Bifurcation and Chaos, 10 (2000) 1171-1266.

[8] **T Takigawa and C. Alzheimer** Phasic and tonic attenuation of EPSPs by inward rectifier K+ channels in rat hippocampal pyramidal cells. J Physiol 539 (2002) 67-75.

[9] **J.M. Nicolaus and P.S. Ulinski** Functional interactions between inwardly rectifying conductances and GABA-mediated inhibition. CNS abstract, (1994)

Krisztina Szalisznyó received her medical degree from Pécs University Medical School (Hungary) in 1997. She was a graduate student at the Department of Biophysics in the Institute of Particle and Nuclear Physics, Budapest. She received her PhD in Computational Neuroscience from Eötvös Lóránd University in 2000. Recently she is a postdoctoral fellow at Ottawa University.

László Zalányi studied physics in Eötvös Lóránd University (Budapest), and received his MSc in statistical physics in 1998. He is a member of the Computational Neuroscience Group at Department of Biophysics in the Institute of Particle and Nuclear Physics since 1997. He started graduate studies at Eötvös Lóránd University in Biophysics in 1998.


A
150 (mV)
−50
200 (pA)
B
150 (Hz)
−50
200 (pA)

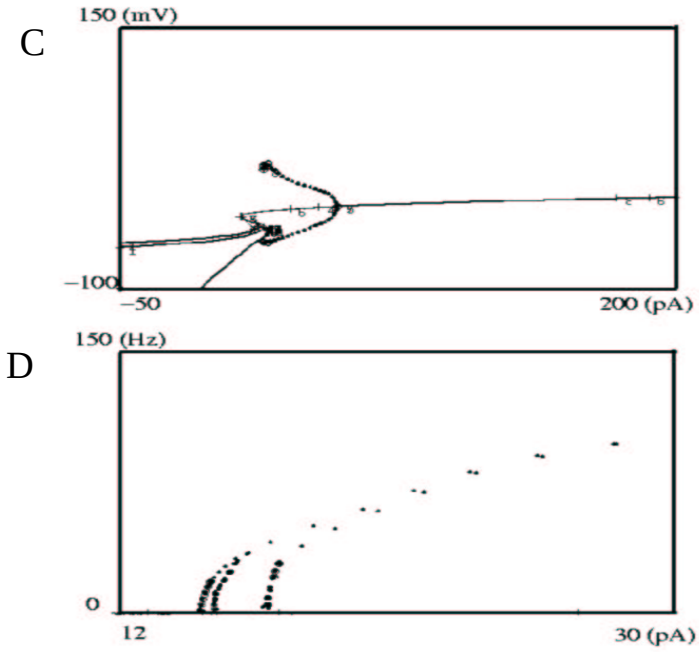
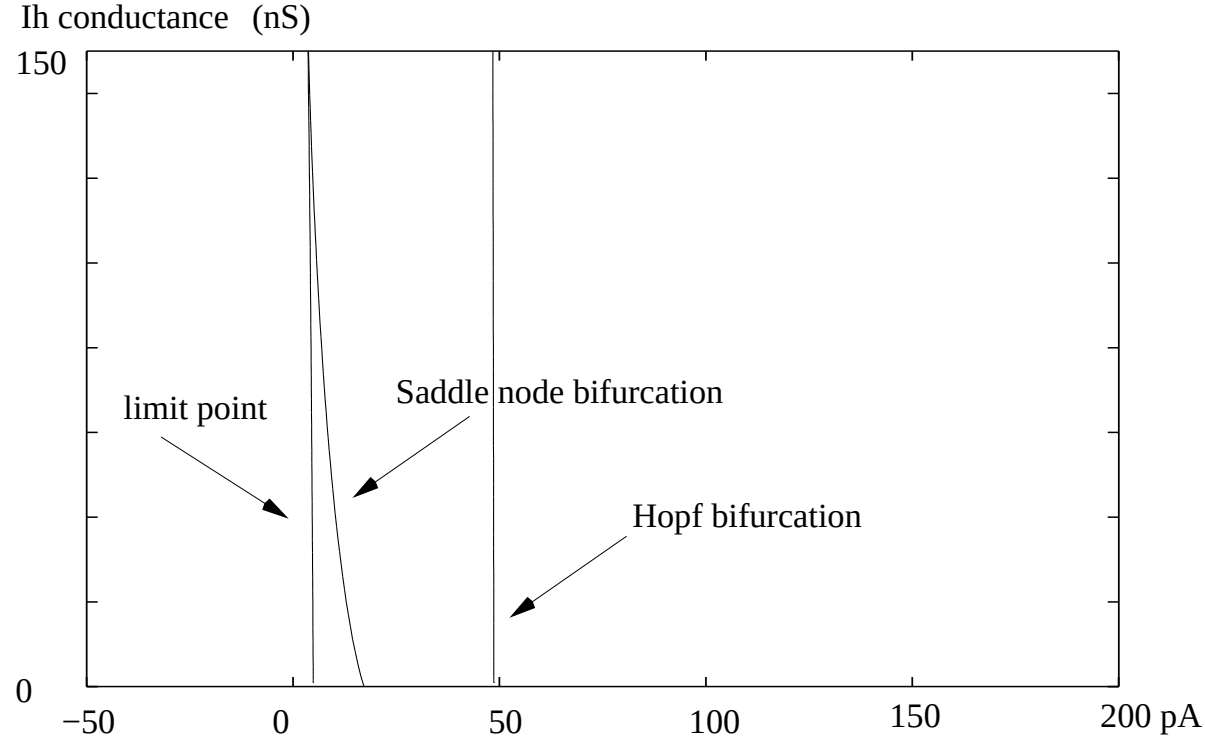

C
150 (mV)
−100
−50
200 (pA)
D
150 (Hz)
0
12
30 (pA)

Figure 2:


Ih conductance (nS)
150
0
limit point
Saddle node bifurcation
Hopf bifurcation
−50
0
50
100
150
200 pA

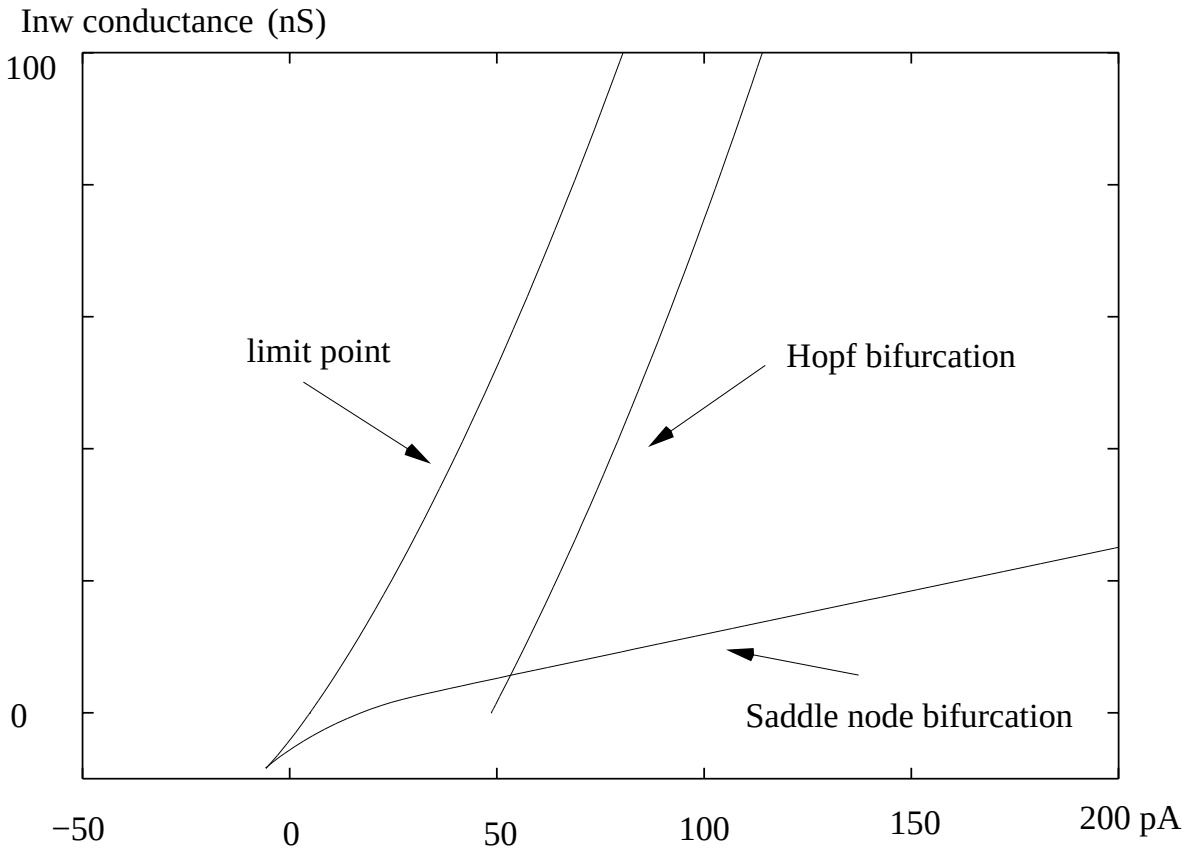

Inw conductance (nS)
100
0
limit point
Hopf bifurcation
Saddle node bifurcation
−50
0
50
100
150
200 pA

Figure 3: