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THE EFFECT OF VARIATIONS IN SODIUM CONDUCTANCES ON PACEMAKING IN A DOPAMINERGIC RETINAL NEURON MODEL

SHORT COMMUNICATION

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Dopaminergic neurons in the retina show spontaneous tetrodotoxin-sensitive pacemaking, which has been explained by a reduced Hodgkin–Huxley-type computer model. The present study used this model to investigate the effect of variations in transient and persistent sodium conductance values on pacemaking, under variable leakage conductance levels. This study indicated that transient sodium conductance plays an indispensable role in pacemaking, which occurs under conditions in which only a persistent sodium conductance is considerably reduced, thus contributing to a detailed understanding of the relationship between sodium conductance and pacemaking.

Keywords: Dopaminergic retinal neurons – pacemaking – model – persistent sodium conductance – transient sodium conductance

Dopaminergic local circuit neurons in the retina (DA cells) which play a critical role in visual adaptation show spontaneous tetrodotoxin-sensitive pacemaking, which has been explained using a reduced computer model based on Hodgkin–Huxley-type formalism [6]. The model contains five ionic conductances: a persistent sodium conductance, a transient sodium conductance, a leakage conductance (g_L), and two potassium conductances. A previous study predicted the effect of the absence of sodium conductance on the pacemaking of model DA cells [6]. Furthermore, the effect of an increase in g_L on pacemaking was analyzed. The increase in g_L hyperpolarizes the model DA cells, which mimics the tonic inhibition of DA cells by GABAergic interneurons [3–5]. However, the previous investigation did not demonstrate the effect of variable sodium conductance levels on pacemaking. The relationship between pacemaking and sodium currents is a subject of intense investigation [1, 6], and the answer to this question will contribute to detailed understanding of this relationship. In the present study, a reduced computer model of DA cells was used to investigate the effect of variations in sodium conductance on pacemaking.

The model DA cell used in this study was based on a previous study (see Fig. 4 in [6]). The modeled cells are solitary dopaminergic amacrines in mouse retina. Among the parameters of the model, only g_L, g_{NaP} and g_{NaT} were varied (g_{NaP} indicates the

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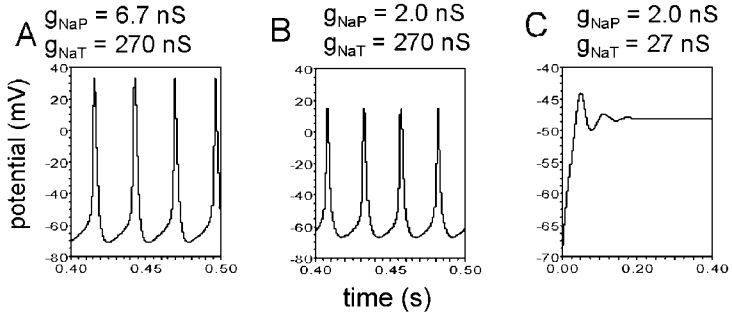

Fig. 1. Membrane potential trajectories of the model DA cell at variable sodium conductance values. **A.** g_{NaP} = 6.7 nS and g_{NaT} = 270 nS. **B.** g_{NaP} = 2.0 nS and g_{NaT} = 270 nS. **C.** g_{NaP} = 2.0 nS and g_{NaT} = 27 nS. In all cases, g_L is at its control value (0.4 nS)

maximal value of a persistent sodium conductance and g_{NaT} the maximal value of a transient sodium conductance). Control values were g_L = 0.4 nS, g_{NaP} = 6.7 nS and g_{NaT} = 270 nS. Other parameters were identical to those in the previous study (see Table 1 in [6]). The free software Scilab (http://www.scilab.org/) was used to simulate the model. The model cell was considered to show pacemaking if the membrane potential oscillation continued for 2.5 s.

When g_L, g_{NaP} and g_{NaT} were at their control values (Fig. 1A), the model DA cell showed pacemaking as described previously [6]. Even if only g_{NaP} was reduced to 30% of its control value, the model cell still showed pacemaking (Fig. 1B). However, when g_{NaT} was also reduced, the model cell did not show pacemaking (Fig. 1C). Based on the plot (Fig. 2A), which illustrates whether pacemaking occurs as a function of g_{NaP} and g_{NaT} when g_L is at its control value, we consider three types of g_{NaP} ranges: (1) a g_{NaP} range that does not support pacemaking even if g_{NaT} is maximum, (2) a g_{NaP} range that supports pacemaking dependently on g_{NaT}, and (3) a g_{NaP} range that supports pacemaking independently of g_{NaT}. Decrease in g_L (Fig. 2B) shifts the border between (1) and (2), but not that between (2) and (3), to a lower value. Increase in g_L (Fig. 2C, D, and E) shifts the borders between (1) and (2) and (2) and (3) to a higher value, and subsequently, (3) disappears and all the g_{NaP} values fall within either (1) or (2).

The present study is important because it is the first to systematically examine the relationship between the sodium conductance levels and pacemaking. As indicated in the previous study, if both g_{NaP} and g_L are at their control values, pacemaking occurs in the absence of g_{NaT} (see Fig. 7 in [6]). However, in the previous study the relationship between g_{NaT} and pacemaking when g_{NaP} was varied with g_L at its control value was not clear. Pacemaking can occur even when g_{NaP} is considerably reduced with g_{NaT} and g_L at their control values. An interesting and novel finding in this study is that g_{NaT} plays an indispensable role in pacemaking under such conditions. This finding contributes to detailed understanding of g_{NaT} roles. In addition, the effect of g_L on g_{NaP}-g_{NaT} pairs that support pacemaking, which was not described in detail previously [6], is revealed in this study. Although it is not technically easy to completely

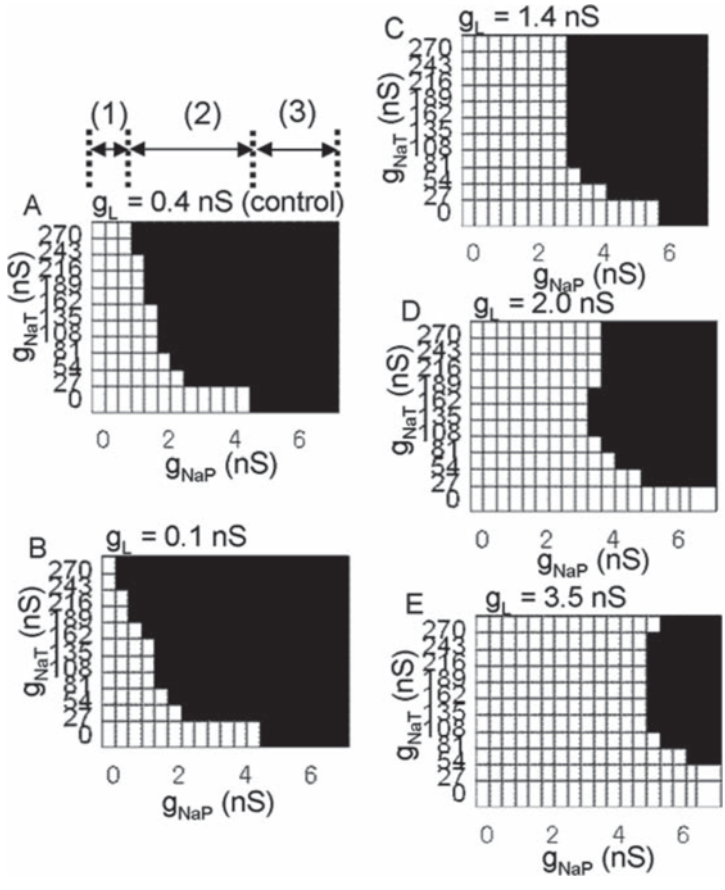

Fig. 2. The behavior of the model DA cell as a function of g_{NaP} and g_{NaT}. **A.** g_L = 0.4 nS (control value). **B.** g_L = 0.1 nS. **C.** g_L = 1.4 nS. **D.** g_L = 2.0 nS. **E.** g_L = 3.5 nS. g_{NaP}–g_{NaT} pairs at which the model cell shows pacemaking are indicated as ■, while those at which it does not show pacemaking are indicated as □. (1) indicates the non-pacemaking range of g_{NaP}, (2) the g_{NaT} -dependent pacemaking range of g_{NaP}, and (3) the g_{NaT} -independent pacemaking range of g_{NaP}

regulate the level of sodium conductance individually in an electrophysiological experiment, the computer model used here allows us to efficiently investigate the effect of variation in sodium conductance values on pacemaking in detail. A more detailed model which incorporates additional conductances was developed in a later study [7]. However, additional conductances only influence the shape and frequency of action potentials, and pacemaking can occur even in the absence of these conductances [1, 2, 7]. Therefore, the present study focused on a reduced model. Calcium channels which are present on DA cells affect the width of action potentials [7]. However, since pacemaking persists even after calcium in the extracellular solution is replaced by cobalt, calcium conductance is not indispensable to pacemaking.

In conclusion, this study indicated that transient sodium conductance plays an indispensable role in pacemaking, which occurs under conditions in which only a persistent sodium conductance is considerably reduced.

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