We investigated the kinetic properties of the hyperpolarization-activated inward current ($I_h$) of thalamocortical (TC) neurons. Recently, it was shown that this current is characterized by different time constants of activation and inactivation, which was in apparent conflict with the single-exponential time course of the current. We introduce here a model of $I_h$, based on the cooperation of a slow and a fast activation variable and show that this kinetic scheme accounts for these apparently conflicting experimental data. We also report that following the combination of such a current with other currents seen in TC cells, one observes several types of oscillating behavior, similar to the slow oscillations and the spindle-like oscillations seen in vitro.

**Key words:** Thalamus; Sleep; Lateral geniculate nucleus; Biophysical model; Hodgkin-Huxley formalism; Slow oscillations; Spindle-like oscillations; Low-threshold calcium current; Inward rectifier; Potassium currents

### A model of the inward current $I_h$ and its possible role in thalamocortical oscillations

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**Introduction**

During wakefulness, the essential role of thalamo...
\[
\frac{dE}{dt} = \frac{(H_v(V) - E)}{\tau_e(V)} \\
\frac{dS}{dt} = \frac{(H_v(V) - S)}{\tau_e(V)}
\]

where the activation function \(H_v(V)\) is estimated such as \(H_v\) fits the data points obtained in reference 2 (see Table 1). The time constants \(\tau_e(V)\) and \(\tau_o(V)\) are estimated from a numerical simulation of voltage clamp protocols (cf. Results section and Table 1).

For simulating membrane potential oscillations, the following equation is used:

\[
C_m \frac{dV}{dt} = -g_L(V - V_L) - I_T - I_k - I_{k2}
\]

where \(C_m = 1 \text{ mF/cm}^2\) is the specific capacity of the membrane, \(g_L = 0.05 \text{ mS/cm}^2\) and \(V_L = -85 \text{ mV}\) are respectively the leak conductance and the leakage potential. \(g_L\) is estimated such as to get a time constant of 20 ms, and \(V_L\) is adjusted such as to obtain a reasonable value of the membrane potential, in the range of −70 to −60 mV. \(I_T\) represents the low-threshold calcium current, characterized by Coulter et al., and \(I_{k2}\) represents the slow potassium current, characterized by Huguenard and Prince. For these two currents, models have been developed and the same models will be used here (cf. reference 14 for \(I_T\), and reference 15 for \(I_{k2}\)). As in the experiments of McCormick and Pape, the temperature is set to 36°C by assuming \(Q_10\) values of 5 and 3 for \(I_T\), and of 2.6 for \(I_{k2}\), and the screening charge effect is calculated assuming an extracellular calcium concentration of 2 mM (cf reference 14).

Conductance values and reversal potentials are estimated from the literature. However, it must be pointed out that, for each one of the three currents considered here, the value of the maximal conductance and the reversal potential are interrelated. For example, if \(V_L\) is increased, \(g_L\) must be decreased to recover similar type of behavior. Therefore, as these parameters are not known with high accuracy, a broad range of these values must be tested. The values of maximal conductances given in the following must be considered as representative of the system, and we verified that similar type of behavior is obtained for a wide range of these parameters.

The differential equations were integrated numerically, using a fifth order, variable-step integration subroutine, provided by the CERN library (MERSON D208) with a fixed accuracy of 0.00001%. The minimal integration step was of the order of 10⁻² to 10⁻³ ms.

Comparison between single and double precision results showed that single precision is sufficient for integration of equations 1–4.

All numerical integrations were performed using Fortran 77 and C programming languages. Sony NWS 3410, Apollo 400 or MIPS 3000 workstations were used. The typical time taken by a simulation of 10 s was of the order of 8–12 s CPU time.

**Results**

Voltage-clamp experiments show that time constants of \(I_A\) obtained during activation may be considerably different from that measured from deactivation at the same membrane potential. On activation, rather slow time constants were seen whereas deactivation appeared to proceed much faster. Only complex kinetic schemes may account for such data. On the other hand, the time course of \(I_A\) follows a single exponential and suggests a simple kinetic description involving one activation variable. In this latter case, however, time constants of activation must be rigorously identical to those of inactivation.

One possible way of solving this conflict is by considering double activation kinetics for \(I_A\). Let us assume that two distinct activation variables characterize the kinetics of \(I_A\), namely \(F\) (fast activation) and \(S\) (slow activation), such that the current is proportional to the product \(SF\). These activation variables are characterized by the same activation function, and by time constants of different magnitudes.

During activation, the two variables \(S\) and \(F\) are initially close to zero. As the voltage is clamped to a value where \(S\) and \(F\) activate, the fast variable \(F\) rapidly increases to its stationary value whereas \(S\) reaches the same value much more slowly. As \(I_A\) is proportional to the product \(SF\), the time course of the measured current will essentially follow the activation kinetics of the variable \(S\) (Fig. 1a). On the other hand, in a deactivation experiment, the two variables are initially close to 1. When the voltage is clamped to a value where \(S\) and \(F\) deactivate, the same scenario as above is seen: \(F\) rapidly reaches its stationary value whereas \(S\) decreases much more slowly. In this case, however, the initial decrease of \(F\) will also lead to an immediate decrease of \(I_A\). Therefore, on deactivation, the time course of the measured current will essentially follow the kinetics of the fast variable (Fig. 1b).

A simulation of voltage-clamp experiments on \(I_A\) (Fig. 1a-b) shows that the time course of current corresponds to a sum of two exponentials. However, usually only one component is prominent in this sum, so the current can be fitted with a single exponential. This could explain the apparent single exponential curves observed experimentally. Figure 1c shows that such a two variable activation kinetic scheme may account for the difference between activation and deactivation kinetics. Although it does not account rigorously for all ex-

<table>
<thead>
<tr>
<th>Function name</th>
<th>Function value</th>
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<tbody>
<tr>
<td>Activation function</td>
<td>(H_v(V) = (1 + 1 \exp (</td>
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<tr>
<td>Slow time constant</td>
<td>(\tau_e(V) = 1 \exp (</td>
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<tr>
<td>Fast time constant</td>
<td>(\tau_e(V) = 1 \exp (</td>
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the membrane slowly hyperpolarizes, and the transformation of spindle-like oscillations into slow oscillations following a depolarizing current step (not shown). However, the frequency of intraspindle oscillations is higher in the model than in experiments at the same temperature. Several modifications should improve this model. First, only three currents were included in our simulations. In the presence of other currents, such as the persistent sodium current or other potassium currents, spindle-like oscillations could occur at more hyperpolarized membrane potentials, where the kinetics of \( I_T \) are slower. Second, the effects of intracellular calcium have been neglected. Experiments on sino-atrial node cells suggest that intracellular calcium shifts the voltage dependence of the activation function \( I_T \). As this modulation occurs on relatively slow time scales, then if the same effect can be shown in TC cells, it could constitute an important element which might contribute to spindle-like oscillatory behavior.

Finally, TC cell simulations using the double activation model of \( I_T \) reproduce a similar sequence of oscillating and resting states, as seen experimentally by the experiments of Solstesz et al.14 The transition between these modes is achieved by increasing the maximal conductance of \( I_T \). The model therefore produces several modes very similar to those seen in TC cells, and the transitions between them.

Conclusions

The model of the hyperpolarization-activated inward current proposed here is based on the cooperation of two activation variables, and accounts for the unusual kinetic properties of this current. This model also preserves the slow components of activation of this current. Different types of oscillating behavior are seen when combining this model of \( I_T \) with known models of two other currents of TC neurons, namely \( I_f \) and \( I_{K2} \). Among these, are slow oscillations and spindle-like oscillations. The latter can be obtained only when considering the double activation model for \( I_T \), which suggests that the slow components of the activation of \( I_T \) might be essential for reproducing spindle-like oscillatory behavior.

References


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