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 thalamocortical (TC) neurons is to provide an efficient relay of incoming sensory information towards the cortex. During synchronized sleep, the same neurons are characterized by several types of membrane potential oscillations which render thalamic neurons considerably less receptive to other stimuli. It is believed that the onset of this oscillatory mode depends both on network properties and the modulation of intrinsic currents in these neurons.

The study of electrophysiological properties of single TC neurons in vitro reveals several types of spontaneous oscillations. Slow oscillations (0.5–2.9 Hz) are commonly seen in cat and rat TC neurons and constitute the spontaneous activity of some of these neurons in vitro. Similar slow oscillations have been observed in vivo in TC neurons during slow wave sleep. Another type of oscillating behavior, termed spindle-like oscillations, has also been observed in cat TC cells in vitro. These oscillations are characterized by bursts of slow oscillations (0.5–3.2 Hz), separated by relatively long periods (5–25 s) during which the have also been described and might have an important role in oscillatory behaviour.

In this paper, we focus on the kinetic description of the inward current $I_h$ as described by voltage clamp experiments by McCormick and Pape. The essential features of this current are that it is noninactivating and it is activated by hyperpolarization below threshold. It also has unusual kinetic properties. At a given membrane potential, the time constant of activation may be different from the time constant of deactivation, which suggests complex kinetics. This observation is not consistent with the single exponential time course of $I_h$, which suggests a simple kinetic scheme. We introduce here a kinetic scheme that accounts for voltage-clamp data and explains this apparent contradiction. We also investigate the oscillatory behavior seen in a single compartment model of the TC cell, including this model of $I_h$ as well as other currents.

Materials and Methods

In all simulations presented here, the cell is considered as a single compartment, and the variations of
\[
\frac{dF}{dt} = \frac{(H_e(V) - F)}{\tau_e(V)} \quad [2]
\]

\[
\frac{dS}{dt} = \frac{(H_e(V) - S)}{\tau_s(V)} \quad [3]
\]

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

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

\[
C_m \frac{dV}{dt} = -g_l(V - V_l) - I_r - I_s - I_{k2} \quad [4]
\]

where \(C_m = 1 \ \mu F/cm^2\) is the specific capacity of the membrane, \(g_l = 0.05 \ \text{mS/cm}^2\) and \(V_l = -85 \ \text{mV}\) are respectively the leakage 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 \(-60 \ \text{mV}^\dagger\). \(I_r\) represents the low-threshold calcium current, characterized by Coupier et al., and \(I_{k2}\) represents the slow potassium current, characterized by Huguenard and Prince.\(^\ddagger\) For these two currents, models have been developed and the same models will be used here (cf. reference 14 for \(I_s\), and reference 15 for \((I_{k2})\)). As in the experiments of McCormick and Pape,\(^\ddagger\) the temperature is set to 36\(^\circ\)C by assuming Q10 values of 5 and 3 for \(I_s\), and of 2.6 for \(I_{k2}\).\(^\ddagger\) The screening charge effect is calculated assuming an extracellular calcium concentration of 2.4 mM (cf. reference 16).

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\(^1\) show that time constants of \(I_s\) 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 \(I_s\) 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 \(I_s\). Let us assume that two distinct activation variables characterize the kinetics of \(I_s\), 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
Modeling I, in thalamocortical neurons

(a) (b) cells. Moreover, for cat TC cells, spindle-like oscillations...
the membrane slowly hyperpolarizes, and the transformation of spindelike 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 \( I_f \) 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 \( I_f \). 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 \( I_f \) reproduce a similar sequence of oscillating and resting states, as seen experimentally by the experiments of Solstes et al. The transition between these modes is achieved by increasing the maximal conductance of \( I_f \). 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 \( I_f \) with known models of other currents of TC neurons, namely \( I_f \) and \( I_{k_2} \). Among these, are slow oscillations and spindle-like oscillations. The latter can be obtained only when considering the double activation model for \( I_f \), which suggests that the slow components of the activation of \( I_f \) might be essential for reproducing spindle-like oscillatory behavior.

**References**


ACKNOWLEDGEMENTS: This research was partly supported by the Belgian Government (ARC and IM.PULS, project RFO AI 10), and by the E.C.E. (ESPRIT, Basic Research, project 3234). We acknowledge Drs Diego Contestros, David McCormick, Terrence Sejnowski and Mircea Steriade for stimulating discussions.

Received 26 November 1992; accepted 2 December 1992