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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 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.[1]

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[2,3] 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.[4] Another type of oscillating behavior, termed spindle-like oscillations, has also been observed in cat TC cells *in vitro*.[3] 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 membrane is silent and hyperpolarizes slowly. However, these oscillations differ significantly from the oscillations recorded *in vivo* during sleep spindles, which originate probably in the reticular nucleus.[5]

Voltage-clamp studies of TC neurons revealed the presence of several currents which are thought to be responsible for these oscillations. First, the low-threshold calcium current I_T, initially described by Jahnsen and Llinas,[6] recently was fully characterized.[7] Another current which was shown to be of central importance for oscillating behavior is the hyperpolarization-activated inward current I_h, characterized by McCormick and Pape.[2] Several potassium currents have also been described[8–11] 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.[2] 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 the membrane potential are obtained through the numerical resolution of kinetic equations following the standard Hodgkin-Huxley scheme.[12]

For simulating voltage-clamp experiment on I_h, the equation used is:

$$I_h = \bar{g}_h \, F \, S \, (V - V_h) \quad [1]$$

where V is the membrane potential at which the cell is clamped (in mV), $\bar{g}_h$ is the maximal conductance of I_h (in mS/cm^2), $V_h = -43$ mV is the reversal potential of I_h.[2] S and F are the activation variables associated to this current. These variables are described by the following first-order equations:

$$\frac{dF}{dt} = (H_\infty(V) - F) / \tau_F(V) \quad [2]$$

$$\frac{dS}{dt} = (H_\infty(V) - S) / \tau_S(V) \quad [3]$$

where the activation function $H_\infty(V)$ is estimated such as $H^2\infty$ fits the data points obtained in reference 2 (see Table 1). The time constants $\tau_F(V)$ 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:

$$C_m \frac{dV}{dt} = -g_L (V - V_L) - I_T - I_h - I_{K2} \quad [4]$$

where $C_m = 1$ μF/cm² is the specific capacity of the membrane, $g_L = 0.05$ mS/cm² and $V_L = -85$ 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 mV.[13] I_T represents the low-threshold calcium current, characterized by Coulter *et al*,[7] and I_{K2} represents the slow potassium current, characterized by Huguenard and Prince.[9] 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,[2] the temperature is set to 36°C by assuming Q_{10} values of 5 and 3 for I_T,[7] and of 2.6 for I_{K2}.[9] 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_h is increased, $\bar{g}_h$ 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.

Table 1. Activation function and time constants of I_h

Function name	Function value
Activation function	$H_\infty(V) = 1/(1 + \exp[(V + 68.9)/6.5])$
Slow time constant	$\tau_S(V) = \exp[(V + 183.6)/15.24]$
Fast time constant	$\tau_F(V) = \exp[(V + 158.6)/11.2]/(1 + \exp[(V + 75)/5.5])$

Results

Voltage-clamp experiments[2] show that time constants of I_h 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_h 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_h. Let us assume that two distinct activation variables characterize the kinetics of I_h, 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_h 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 more slowly. In this case, however, the initial decrease of F will also lead to an immediate decrease of I_h. 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_h (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-

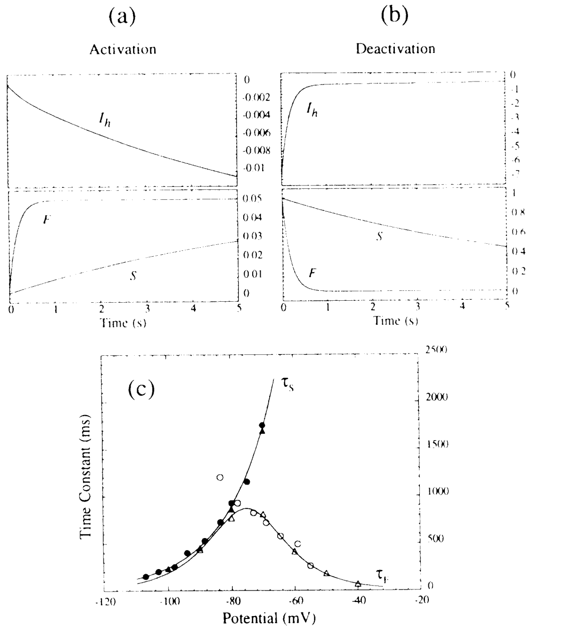

FIG. 1. Simulation of voltage clamp protocols on the double activation model of I_h. (**a**) activation of I_h. The voltage is initially of − 30 mV and the current is recorded after the voltage is clamped to − 50 mV. Time courses of the current I_h ($\bar{g}_h$ = 1 mS/cm²) and of the activation variables *F* and *S* are displayed. The slow exponential time course of the variable *S* is followed by the current and the estimated time constant is of 3013.1 ms. (**b**) deactivation of I_h. Same protocol as in (a), except that the initial voltage is of − 110 mV. In this case, although the membrane is clamped to the same voltage as in (a), the current follows the faster time course of variable *F*, and a small time constant of 182.7 ms is measured. (**c**) time constants obtained for activation and deactivation of I_h as a function of the membrane potential. Circles indicate experimental data obtained by McCormick and Pape during activation (filled circles) and deactivation (open circles). Triangles represent time constants estimated from a single exponential fitting of currents illustrated in (a) and (b) (filled triangles = activation, open triangles = deactivation). Solid lines represent the functions used for modeling the time constants of I_h (cf Table 1).

perimental data points, the slow components of the time constant of activation are well represented in this model.

The time constant $\tau_s(V)$ is chosen by an exponential fit of experimental data of activation, whereas $\tau_F(V)$ is fitted as a bell-shaped function as close as possible to experimental data of deactivation process. These functions are listed in Table 1. We now investigate the oscillatory behavior seen in a single compartment model of the TC cell, including the model of I_h described above, as well as the leakage current, the low threshold current I_T and the slow potassium current I_{K2} (cf Materials and Methods).

In vitro experiments have shown that although some TC neurons are spontaneously oscillating, the presence and the pattern of oscillations strongly depends on I_h. Blocking I_h by application of caesium results in the abolition of slow oscillations and the membrane lies in a hyperpolarized resting potential.[2,16] On the other hand, enhancement of I_h by application of noradrenaline usually abolishes slow oscillations resulting in a depolarized resting potential, close to firing threshold.[16,17] Such a depolarized resting state is probably adequate for describing the relay mode of thalamic cells. Moreover, for cat TC cells, spindle-like oscillations have also been found when enhancing I_h.[16] In this case, while increasing I_h strength, the following sequence of modes were observed: a hyperpolarized resting state when I_h is blocked, slow oscillations for weak values of I_h, spindle-like oscillations for higher values of I_h and finally, a depolarized resting state for a further increase in the value of I_h. This sequence was reversed by gradually decreasing the strength of I_h.

A similar sequence of oscillatory modes can be seen in the model as the maximal conductance of I_h is decreased. As shown in Figure 2, for the highest values of $\bar{g}_h$, the membrane lies in a depolarized resting state close to − 60 mV. Decreasing $\bar{g}_h$ leads to spindle-like oscillations (intraspindle frequency of 10–14 Hz and a period of approximately 9 s). As $\bar{g}_h$ is decreased further, one observes oscillations of a lower frequency around 1.1 Hz. Finally, for the weakest values of $\bar{g}_h$, the membrane switches to a hyperpolarized resting state, close to − 80 mV.

Discussion

We have proposed a double activation model of the hyperpolarization-activated current I_h. This model accounts for voltage clamp data for this current while preserving the slow component of activation of the current, which would be lost in a single activation model. We believe that this slow component is important for the intrinsic properties of thalamocortical neurons. It must be pointed out that, in addition to thalamic cells,[2,16] such slow components have been observed during activation of a very similar current in crustacean motor neurons[18] and in sinoatrial node cells.[19]

The slow oscillations of TC cells are thought to depend on the interaction between I_T and I_h.[2,16] This hypothesis has been confirmed by modeling studies of these two currents.[20–22] The model proposed here for I_h also accounts for the production of such slow oscillations when combined with I_T (not shown). No spindle-like oscillations were reported in previous modeling studies, although some of them take into account a large variety of currents.[20,22] Oscillations endowed with some features of the spindle-like oscillations are observed when the double activation model of I_h is combined with I_T and the slow potassium current I_{K2}. In addition, it must be pointed out that when considering a single-activation model of I_h (cf reference 15), we were unable to find spindle-like oscillating behavior from the same combination of currents. One possible explanation is that for single activation models of I_h, the slow time constants of activation are not reproduced. It is likely that these components are essential for producing spindle-like behavior.

The main features of spindle-like oscillations are the presence of short bursts of calcium spikes lasting 2 to 5 s, long silent interbursts phases (5–25 s) during which

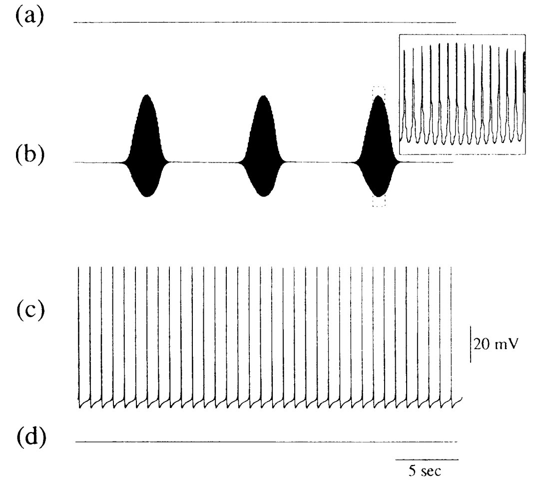

FIG. 2. Different types of oscillatory behavior obtained from the double activation model of I_h combined with I_T and I_{K2}. The same values of the conductances of I_T and I_{K2} are used here ($\bar{g}_T$ = 1.75 mS/cm², $\bar{g}_{K2}$ = 3 mS/cm²) and different modes can be seen for decreasing values of the maximal conductance of I_h. (**a**) depolarized resting state around − 57 mV for $\bar{g}_h$ = 1 mS/cm², (**b**) spindle-like oscillations for $\bar{g}_h$ = 0.4 mS/cm², (**c**) slow oscillations for $\bar{g}_h$ = 0.002 mS/cm², (**d**) hyperpolarized resting state around − 82 mV for $\bar{g}_h$ = 0. Inset in (b): oscillations delimited by the dashed line are shown at higher temporal resolution (magnification of 10).

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[6] or other potassium currents,[11] 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[23] suggest that intracellular calcium shifts the voltage dependence of the activation function I_h. 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_h reproduce a similar sequence of oscillating and resting states, as seen experimentally by the experiments of Solstesz *et al.*[16] The transition between these modes is achieved by increasing the maximal conductance of I_h. 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_h with known models of two other currents of TC neurons, namely I_T 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_h, which suggests that the slow components of the activation of I_h might be essential for reproducing spindle-like oscillatory behavior.

References

1. Steriade M and Llinas RR. *Physiol Reviews* **68**, 649–742 (1988).
2. McCormick DA and Pape HC. *J Physiol* **431**, 291–318 (1990).
3. Leresche N, Lightowler S, Soltesz I *et al. J Physiol* **441**, 155–174 (1991).
4. Curro Dossi R, Nunez A and Steriade M. *J Physiol* **447**, 215–234 (1992).
5. Steriade M and Deschênes M. *Brain Res Reviews* **8**, 1–63 (1984).
6. Jahnsen H and Llinas RR. *J Physiol* **349**, 227–247 (1984).
7. Coulter DA, Huguenard JR and Prince DA. *J Physiol* **414**, 587–604 (1989).
8. Huguenard JR, Coulter DA and Prince DA. *J Neurophysiol* **66**, 1305–1315 (1991).
9. Huguenard JR and Prince DA. *J Neurophysiol* **66**, 1316–1328 (1991).
10. McCormick DA. *J Neurophysiol* **66**, 1176–1189 (1991).
11. Budde T, Mayer R and Pape HC. *Eur J Neurosci* **4**, 708–722 (1992).
12. Hodgkin AL and Huxley AF. *J Physiol* **117**, 500–544 (1952).
13. Jahnsen H and Llinas RR. *J Physiol* **349**, 205–226 (1984).
14. Wang XJ, Rinzel J and Rogawski MA. *J Neurophysiol* **66**, 839–850 (1991).
15. Huguenard JR and McCormick DA. *J Neurophysiol* **68**, 1373–1383 (1992).
16. Soltesz I, Lightowler S, Leresche N *et al. J Physiol* **441**, 175–197 (1991).
17. McCormick DA and Pape HC. *J Physiol* **431**, 319–342 (1990).
18. Kiehn O and Harris-Warrick RM. *J Neurophysiol* **68**, 496–508 (1992).
19. van Ginneken ACG and Giles W. *J Physiol* **434**, 57–83 (1991).
20. Lytton W and Sejnowski TJ. *J Neurophysiol* **66**, 1059–1079 (1991).
21. Toth T and Crunelli V. *NeuroReport* **3**, 65–68 (1992).
22. McCormick DA and Huguenard JR. *J Neurophysiol* **68**, 1384–1400 (1992).
23. Hagiwara N and Irishawa H. *J Physiol* **409**, 121–141 (1989).

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