Ionic Mechanisms for Intrinsic Slow Oscillations in Thalamic Relay Neurons

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ABSTRACT The oscillatory properties of single thalamicocortical neurons were investigated by using a Hodgkin-Huxley-like model that included Ca$^{2+}$ diffusion, the low-threshold Ca$^{2+}$ current ($I_T$) and the hyperpolarization-activated inward current ($I_h$). $I_h$ was modeled by double activation kinetics regulated by intracellular Ca$^{2+}$. The model exhibited waxing and waning oscillations consisting of 1–25-s bursts of slow oscillations (3.5–4 Hz) separated by long silent periods (4–20 s). During the oscillatory phase, the entry of Ca$^{2+}$ progressively shifted the activation function of $I_h$, terminating the oscillations. A similar type of waxing and waning oscillation was also observed, in the absence of Ca$^{2+}$ regulation of $I_h$, from the combination of $I_T$, $I_h$, and a slow K$^+$ current. Singular approximation showed that for both models, the activation variables of $I_h$ controlled the dynamics of thalamocortical cells. Dynamical analysis of the system in a phase plane diagram showed that waxing and waning oscillations arose when $I_h$ entrained the system alternately between stationary and oscillating branches.

INTRODUCTION

The thalamus is central to the generation of oscillatory activity during slow wave sleep. Two types of rhythmical activities of the electroencephalogram have been characterized, spindle waves (7–14 Hz) and delta waves (0.5–4 Hz). Spindle waves depend on both intrinsic and network mechanisms in the thalamus (Steriade and Deschenes, 1984; Steriade and Llinás, 1988). Until recently (Steriade et al., 1990) delta waves were assumed to originate in the cortex. However, a recent study conducted in cat in vivo (Curro Dossi et al., 1992; Nunez et al., 1992) showed that the thalamus can generate spontaneous oscillations of 0.5–4 Hz even after sev-
based on voltage-clamp data of $I_T$ and $I_R$. Special emphasis is given to uncovering the role of $I_0$ in organizing the transitions between multiple oscillatory and resting states of the TC cell.

**MATERIALS AND METHODS**

Our single compartment model of a TC cell used a Hodgkin-Huxley-type scheme (Hodgkin and Huxley, 1952) for the ionic currents. The equation describing the derivative of the membrane potential $V$ was:

$$C_m \frac{dV}{dt} = -g_l(V - E_l) - I_1 - I_0 - I_{K_2} + I_{ext},$$  \hspace{1cm} (1)

where $C_m = 1 \mu F/cm^2$ is the specific capacity of the membrane, $g_l = 0.05$ mS/cm$^2$, and $E_l = -86$ mV are, respectively, the leakage conductance and the leakage reversal potential. The value of $g_l$ was chosen to obtain a membrane time constant of 20 ms, and $E_l$ was adjusted to match the resting membrane potential to $-60$ mV (Jahnsen and Linas, 1984a) when $I_h$ was present, and to more hyperpolarized levels, when $I_h$ was blocked (McCormick and Pape, 1990b). The total membrane area was assumed to be 1000 $\mu m^2$, the area of a typical TC cell soma. Dendrites were not taken into account.

Only currents absolutely necessary to generate subthreshold oscillations were included in the model. These currents were the low-threshold $Ca^{2+}$ current $I_T$, the hyperpolarization-activated current $I_0$, and the voltage-dependent $K^+$ current $I_{K_2}$. $I_{ext}$ represents the external current applied to the cell. Other Na$^+$ and $K^+$ currents, such as the $I_{Na}$ and $I_K$ responsible for the generation of action potentials, $I_{Na}$, $I_{Na,fast}$, or $I_C$, were not included in the model (for details on these currents see McCormick and Huguenard, 1992).

Kinetic models have been developed previously for $I_T$ (Huguenard and McCormick, 1992; Wang et al., 1991), for $I_0$ (Destexhe and Babiloyantz, 1993; Huguenard and McCormick, 1992), and for $I_{K_2}$ (Huguenard and McCormick, 1992). We use them as our starting point.

### The low-threshold Ca$^{2+}$ current $I_T$

Voltage-clamp experiments (Coulter et al., 1989; Crunelli et al., 1989) show that the dynamical properties of $I_T$ can be accounted for by a Hodgkin-Huxley-type formalism. A four-variable model of this low-threshold current was recently proposed by Wang et al. (1991) and will be used here. The

**TABLE 1 Activation functions and time constants for the voltage-dependent currents $I_T$, $I_0$, and $I_{K_2}$.**

<table>
<thead>
<tr>
<th>Current</th>
<th>Variable</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_T$</td>
<td>$m$</td>
<td>$m_+(V) = 1/{1 + \exp[-(V - 65)/7.8]}$</td>
</tr>
<tr>
<td></td>
<td>$\tau_m$</td>
<td>$\tau_m(V) = 0.15m_+(V)/{1.7 + \exp[-(V + 30.8)/13.5]}$</td>
</tr>
<tr>
<td></td>
<td>$h$</td>
<td>$h = \exp[-(V + 162.3)/17.8]0.26$</td>
</tr>
<tr>
<td></td>
<td>$d$</td>
<td>$d = [\tau_d(V)/[K(V) + 1]]$</td>
</tr>
<tr>
<td></td>
<td>$\tau_d$</td>
<td>$\tau_d(V) = 62.4/{1 + \exp[(V + 39.4)/30]}$</td>
</tr>
<tr>
<td>$I_0$</td>
<td>$S_1$, $F_1$</td>
<td>$H_0(V) = 1/{1 + \exp[(V + 68.9)/6.5]}$</td>
</tr>
<tr>
<td></td>
<td>$\tau_0$</td>
<td>$\tau_0(V) = \exp[(V + 183.6)/15.24]$</td>
</tr>
<tr>
<td></td>
<td>$\gamma_0$</td>
<td>$\gamma_0(V) = \exp[(V + 158.6)/11.2]/(1 + \exp[(V - 75)/5.5])$</td>
</tr>
<tr>
<td>$I_{K_2}$</td>
<td>$m_2$, $m_{2,off}$</td>
<td>$m_{2,off}(V) = 1/{1 + \exp[-(V + 43)/17]}$</td>
</tr>
<tr>
<td></td>
<td>$\tau_{m_2}$</td>
<td>$\tau_{m_2}(V) = 2.86 + 0.29/[\exp(V + 81)/25.6]$</td>
</tr>
<tr>
<td></td>
<td>$h_1$, $h_2$</td>
<td>$h_1 = 1/{1 + \exp[(V + 58)/10.6]}$</td>
</tr>
<tr>
<td></td>
<td>$\tau_{h_1}$</td>
<td>$\tau_{h_1}(V) = 34.65 + 0.29/[\exp(V - 1329)/200]$</td>
</tr>
<tr>
<td></td>
<td>$\gamma_1$</td>
<td>$\gamma_1(V) = \exp[-(V + 130)/7.1]$</td>
</tr>
<tr>
<td></td>
<td>$h_2$</td>
<td>$h_2(V) = \gamma_1(V)$ for $V \geq -70$ mV</td>
</tr>
<tr>
<td></td>
<td>$\tau_{h_2}$</td>
<td>$\tau_{h_2}(V) = 2570$ ms for $V &lt; -70$ mV</td>
</tr>
</tbody>
</table>

These functions were chosen to fit voltage-clamp measurements of these currents. All values were scaled to a temperature of 36°C assuming $Q_{10}$ values of 5 and 3 for $I_T$ (Coulter et al., 1989), and 2.6 for $I_{K_2}$ (Huguenard and Prince, 1991). The screening charge effect was calculated assuming an extracellular Ca$^{2+}$ concentration of 2 mM.

Recently, a kinetic scheme for $I_0$ was introduced to account for the kinetic properties of $I_0$ (Destexhe and Babiloyantz, 1993). Two distinct activation gates were assumed, namely $F$ (fast activation) and $S$ (slow activation) according to the following kinetic scheme:

$$S_{\text{closed}} \xrightleftharpoons{\alpha_{S}}^{\beta_{S}} S_{\text{open}} \quad F_{\text{closed}} \xrightleftharpoons{\alpha_{F}}^{\beta_{F}} F_{\text{open}},$$  \hspace{1cm} (3)

where $S_{\text{closed}}$ and $F_{\text{closed}}$ represent the closed states of the slow and fast activation gates of $I_0$, $S_{\text{open}}$ and $F_{\text{open}}$ represent the open states of these gates, and $\alpha_{S}$, $\beta_{S}$, $\alpha_{F}$, and $\beta_{F}$ are voltage-dependent rate constants (see below).
posed by McCormick (1992), is the regulation of \( I_h \) by binding of intracellular \( \text{Ca}^{2+} \), as found in whole cell voltage-clamp studies of \( I_h \) in sino-atrial node cells (Hagiwara and Irisawa, 1989). Evidence for the control of the voltage-dependent properties of \( I_h \) by intracellular \( \text{Ca}^{2+} \) were also obtained in cat neocortical neurons (Schwindt et al., 1992). As the \( \text{Ca}^{2+} \) dependence of \( I_h \) has not yet been studied in TC cells, it was assumed to be similar to that of sino-atrial node cells.

The activation curve of \( I_h \) in sino-atrial node cells shifts toward more

\[
\text{Ca}^{2+} + P \rightleftharpoons \text{CaP} \rightarrow P + \text{Ca}^{2+},
\]

where \( P \) represents the \( \text{Ca}^{2+} \) pump, \( \text{CaP} \) is an intermediate state, \( \text{Ca}^{2+} \) is the extracellular \( \text{Ca}^{2+} \) concentration, and...
Estimation of the values of parameters

Conductances values and reversal potentials for the above currents were estimated from published values provided by measurements in vitro. However, these data only provide approximate values for these parameters. Also, the complex dendritic geometry of the cell was not taken into account, which would affect these values. For each of the currents considered here, the value of the maximal conductance and the reversal potential are interrelated. For example, if \( E_h \) is increased, \( g_h \) must be decreased to reproduce similar results. We introduced a new set of voltage-dependent conductances to account for these effects.
The shift of the \( I_h \) activation logarithmic in \([Ca]\) and a shift of 13 mV is obtained for \( C = 6.4 \).

The shift should be negligible (\( C < 1 \)) at the resting level, \([Ca] \approx 2 \times 10^{-3} \) mM, which gives a lower bound: \( Ca_{crit} > 2 \times 10^{-4} \) mM. During activation of \( I_T \), the value of \([Ca]\), just beneath the membrane increases to about \( 10^{-2}-10^{-3} \) mM and shifts \( I_h \) by a few millivolts (\( C > 1 \)), which gives an upper bound: \( Ca_{crit} < 10^{-2}-10^{-3} \) mM. In the simulations presented here, we chose \( n = 2 \) and \( Ca_{crit} = 5 \times 10^{-4} \) mM.

**Kinetics of \( I_h \)**

\( I_h \) activates very slowly and its time constant can be greater than 1 s at 3–6°C (McCormick and Pape, 1990a; Soltesz et al., 1991). The time course of \( I_h \) activation may differ considerably from the time course of deactivation at the same membrane potential. Currents similar to \( I_h \) in other preparations also show slow activation and, in some cases, a faster time course for deactivation (for recent studies on \( I_h \), see Erickson et al., 1993; Galligan et al., 1990; Kamondi and Reiner, 1991; Uchimura et al., 1990; van Ginneken and Giles, 1991; and references therein).

Despite the different time constants for activation and deactivation, \( I_h \) follows a single exponential time course, which would suggest a simple description involving first order kinetics. However, in a simple first-order kinetic scheme, the time constant of activation is identical to that of deactivation.

A novel kinetic scheme was proposed (Destexhe and Babloyantz, 1993) to account for these apparently conflicting experimental data (see Materials and Method). We assume that the permeability of \( I_h \) channels depends on two independent gates \((S\) for slow activation and \( F\) for fast activation) which must be opened simultaneously.

This model exhibits two time constants. Following a depolarizing voltage jump, the two gates \( S \) and \( F \), which are initially closed, begin to activate: the fast variable \( F_1 \) rapidly increases to its equilibrium value, whereas \( S_1 \) reaches the same value more slowly. Since \( I_h \) is proportional to the product \( S_1 F_1 \), the time course of the measured current will reflect the activation kinetics of the slow variable \( S_1 \) (Fig. 2 A). The opposite occurs upon a hyperpolarizing voltage jump from a depolarized level where both gates were initially open: \( F_1 \) rapidly closes, while \( S_1 \) closes more slowly. Since the decrease of \( F_1 \) immediately decreases \( I_h \), the time course of deactivation follows the kinetics of the fast variable (Fig. 2 B).

Although in our model for \( I_h \) the current is a product of two exponentials (Eq. 4), the two time constants were sufficiently different that the time course of the current was practically a single exponential. This could explain the single exponential curves observed from voltage-clamp experiments of \( I_h \).

The slow time constant, \( \tau_S(V) \), was chosen by an exponential fit of voltage-clamp measurements of the time constants of activation, whereas the fast time constant \( \tau_F(V) \) was fit by a bell-shaped function from measurements of the deactivation time constants (see Fig. 2 C and Table 1).

Simulation of voltage-clamp experiments using these functions produced curves and measurements indistinguishable from those obtained by McCormick and Pape (1990a) (Fig. 2 C). In particular, the double activation scheme for \( I_h \) deactivates faster than it activates (Destexhe and Babloyantz, 1993).

In the next section, regulation of \( I_h \) by \( Ca^{2+} \) is introduced and its interactions with other currents examined.

**Oscillatory behavior from \( Ca^{2+}\)-regulated \( I_h \)**

Previous models of TC cells have shown that the interaction between \( I_T \) and \( I_h \) supports slow oscillations in the delta range 0.5–4 Hz (Lytton and Scjnowski, 1992; McCormick and Huguenard, 1992; Toth and Crunelli, 1992a). We demonstrate here that this slow oscillation can wax and wane as a result of the interaction between the two subthreshold currents \( I_T \) and \( I_h \), and the regulation of \( I_h \) by intracellular \( Ca^{2+} \).

The double activation model of \( I_h \) combined with \( I_T \) can give rise to a variety of resting states and slow oscillations. These patterns were obtained for different values of the maximal conductance \( g_{h}\) of \( I_h \) (Fig. 3). For the lowest values of \( g_{h} \) (< 0.01 mS/cm²), the model remained in a hyperpolarized resting state at about -84 mV (Fig. 3 A). A similar hyperpolarized resting state has been observed in vitro (McCormick and Pape, 1990a; Soltesz et al., 1991) after blockade of \( I_h \).

For the highest values of this conductance \( (g_{h} > 0.1 mS/cm²) \), there was a more depolarized resting state (around -58 mV close to firing threshold (Fig. 3 D)). The depolarized resting state was similar to that observed in vitro following the enhancement of \( I_h \) by noradrenaline and probably corresponds to the “relay state” of TC neurons (McCormick and Pape, 1990a; Soltesz et al., 1991).

For moderate values of \( g_{h} \), various types of slow oscillatory behavior were observed. In the range of \( g_{h} \) between 0.0018 and 0.02 mS/cm², there was a regular slow oscillation of 0.5–3.5 Hz (Fig. 3 B) similar to the slow oscillatory behavior recorded in TC cells in vitro (McCormick and Pape, 1990a).

For somewhat higher values of \( g_{h} \) (between about 0.02 and 0.09 mS/cm²), waxing and waning oscillations appeared (Fig. 3 C) that consisted of bursts of slow oscillations (typically lasting a few seconds at frequency of 3.5–4 Hz with faster components at 8–9 Hz) separated by a silent phases lasting about 4–20 s. Such bursts of slow oscillations (0.5–3.2 Hz) separated by silent phases (5–25 s) have been recorded in cat TC cells in vitro (Leresche et al., 1990, 1991).

**Properties of \( Ca^{2+}\)-dependent waxing and waning oscillations**

Soltesz et al. (1991) showed that slow oscillations and waxing and waning oscillations observed in cat TC cells are two properties of the slow oscillations consistent with the aforementioned double activation and relaxation of \( I_h \).
states in a continuum and that the transition from slow oscillations to waxing and waning type of rhythmicity could be achieved by enhancement of \( I_h \). The same sequence of oscillations was observed here as \( I_h \) was enhanced in the model (Fig. 3). Other properties of in vitro waxing and waning oscillations include a characteristic hyperpolarization during the silent phase and their transformation into slow oscillations by a depolarizing current step. These properties were also present in our model (Fig. 4, A and B).

The transition from waxing and waning oscillation to slow oscillations from a depolarizing current step was not observed for all values of \( g_h \). For some values of \( g_h \), the opposite was observed: waxing and waning oscillations were transformed into slow oscillations by applying a hyperpolarizing current step (not shown).

There was a progressive hyperpolarization during the silent phase (Fig. 4B). During the burst there was a gradual depolarization that was most clearly seen by averaging the membrane potential (Fig. 4C).

The time courses of the different variables of the model during a waxing and waning sequence are displayed in Fig. 5. The membrane hyperpolarized slowly during the silent phase until \( I_T \) deinactivated and the oscillations began. During the burst of slow oscillations, \( \text{Ca}^{2+} \) entered transiently at the peak of each spike and bound progressively to \( I_h \) channels (reflected in the slow increase of \( S_2 \) and \( F_2 \)). \( \text{Ca}^{2+} \) binding to \( I_h \) channels shifted the \( I_h \) activation curve, producing a gradual depolarization during the oscillatory phase (Fig. 4C). This depolarization prevented \( I_T \) from activating and damped the slow oscillations. During the ensuing silent phase, \( S_2 \) and \( F_2 \) slowly decreased and caused the membrane to hyperpolarize.

The progressive transformation of slow oscillations into waxing and waning oscillations is shown in Fig. 6. A bifur-
cation occurred around $\tilde{g}_h = 0.02 \text{ mS/cm}^2$ from slow oscillations to a state where the slow oscillations were interrupted by short silent phases (Fig. 6 B). As $\tilde{g}_h$ increased, the length of the silent phase increased and the bursts became shorter (Fig. 6, C and D). The frequency inside the oscillatory phase was always comparable to that of the slow oscillations.

The duration of the silent phase and the oscillatory phase as a function of $\tilde{g}_h$ are reported in Fig. 7 A. The occurrence as the depolarized state was approached, with oscillatory phase reducing to a minimum length before disappearing (sometimes a low amplitude periodic oscillation was seen in a very narrow range of $\tilde{g}_h$ before the depolarized state appeared). The period of the slow oscillation decreased with $\tilde{g}_h$ (indicated by S in Fig. 7 A), which is consistent with the slowing down of the slow oscillation observed after progressive blockade of $I_a$ channels.
consistent with the assumption that the binding of $\text{Ca}^{2+}$ is critical for the onset and termination of the oscillatory phase. The silent phase, which depends on the return of $S_2$ and $F_2$ to their resting values, is expected to be proportional to $k_1^{-1}$. The length of the oscillatory phase, which depends on the rate of rise of $S_2$ and $F_2$, is also expected to be proportional to $k_2^{-1}$.

$I_{K2}$-dependent waxing and waning oscillations

The $\text{Ca}^{2+}$-dependent regulation of $I_h$ is not the only way to obtain waxing and waning oscillation with $I_T$ and $I_h$. A second possible mechanism depends on the interaction among $I_T$, $I_h$, and the slow $\text{K}^+$ current $I_{K2}$. $\text{Ca}^{2+}$ mechanisms were not included in this version of the model.

It was reported previously (Destexhe and Bubloyantz, 1993) that the double activation model of $I_h$ showed the same sequence of oscillatory states as in vitro experiments when combined with $I_T$ and $I_{K2}$. This model was explored using different values for some of the parameters. Characteristic properties of waxing and waning oscillations, such as the progressive hyperpolarization during the silent phase and the transformation into slow oscillations by applying a depolarizing current step, were also observed with this model (Fig. 8).

Fig. 9 shows the time course of several gating variables during a waxing and waning sequence. As in the mechanism proposed by Soltesz et al. (1991), $I_h$ activates more and more during each cycle of the oscillatory phase. The resulting depolarization inactivates $I_T$ and the oscillations damp.

Compared with the $\text{Ca}^{2+}$-dependent waxing and waning oscillations, the slow depolarization of the membrane during the oscillatory phase in the $I_{K2}$-dependent model is provided by a more pronounced $I_h$ activation ($S_1$ reaches its maximal value during the oscillatory phase) and inactivation of $I_{K2}$. Progressive deactivation of $I_h$ then hyperpolarizes the membrane.

Waxing and waning oscillations were never observed without adding a slow depolarization-activated outward current in addition to $I_T$ and $I_h$. Similar oscillations were observed when $I_{K2}$ was replaced by slow $\text{K}^+$ currents, such as the slow $\text{Ca}^{2+}$-activated $\text{K}^+$ current or a depolarization-activated noninactivating $\text{K}^+$ current similar to the muscarinic current $I_M$ (not shown). However, these currents are probably not present in TC cells.

Singular approximation of waxing and waning oscillations

Instead of studying the mechanisms of waxing and waning oscillations in terms of activation variables and $\text{Ca}^{2+}$ concentration, it is possible to describe these oscillations as dynamical states of the system. This provides a more global view of “stationary states” or “limit cycle oscillations” of the system. Complex oscillatory processes, such as oscillations

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**FIGURE 5** Time course of the gating variables of $I_h$ during Ca$^{2+}$-dependent waxing and waning oscillations. (A) Slow activation variables $S_1$ and $S_2$. (B) Fast activation variables $F_1$ and $F_2$. (C) Intracellular Ca$^{2+}$ concentration $[\text{Ca}]_i$. (D) Membrane potential $V$, $g_h = 0.04 \text{ mS/cm}^2$. Same parameters as in Fig. 3 C.
the stable limit cycle coexisted with the stable stationary state (Fig. 10 B). The state of the system within this interval of $S_2$ depended on its previous history.
FIGURE 9  Time course of the gating variables of $I_h$ and $I_{K_C}$ and the membrane potential during an $I_{K_C}$-dependent waxing and waning oscillation. (A)
FIGURE 10  Singular approximation applied to the Ca\(^{2+}\)-dependent model of waxing and waning oscillations. (A) For extreme values of the slow variable \(S_2\), treated as a parameter, the system exhibited either slow oscillations (\(S_2 = 0.09\)) or a stable stationary state (\(S_2 = 0.65\)). Other parameters are the same as in Fig. 3C. (B) Bifurcation diagram of the system as a function of \(S_2\). During the slow oscillations of \(S_2\), the system alternated between a slow oscillatory state and a resting state, tracing a hysteresis loop as shown in the diagram. The order of events underlying the waxing and waning sequence are indicated by dotted arrows. Dashed lines represent unstable states (USS, unstable stationary state; ULC, unstable limit cycle), and continuous lines represent stable states (SSS, stable stationary state; SLC, stable limit cycle). (C) Corresponding sequence of events in a single cycle of the waxing and waning oscillations. (D) Trajectories of waxing and waning oscillations in the V/S\(_2\) diagram. Here the full system was simulated without considering \(S_2\) as a parameter. Dashed lines represent the presumed position of oscillatory and stationary branches and dotted arrows depict the same sequence of events as in B.

Irisawa, 1989) and neocortical neurons (Schwindt et al., 1992). These data suggest that intracellular Ca\(^{2+}\) ions directly affect \(I_h\) channels and shift the activation function toward more depolarized potentials. We assumed that the Ca\(^{2+}\) dependency of \(I_h\) is caused by direct binding of Ca\(^{2+}\) ions on a function of \(I_h\) by a few millivolts (McCormick and Pape, 1990b). We did not include this shift in our simulations.

We also found intermediate patterns of oscillations which were not reported experimentally. Close to the transition between slow oscillations and waxing and waning oscillations.
tonic firing, slow oscillations, and waxing and waning oscillations in TC cells. Experiments can be designed to test which of the two proposed mechanisms is responsible for the oscillations. The higher frequency of the $I_{K3}$-dependent model makes it less plausible than the $Ca^{2+}$-dependent model. The $I_{K3}$-dependent model predicts that the waxing

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