Ionic Mechanisms for Intrinsic Slow Oscillations in Thalamic Relay Neurons

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ABSTRACT The oscillatory properties of single thalamocortical 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 rhythmic 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 Llinas, 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 (Curró Dossi et al., 1992; Nunez et al., 1992) showed that the thalamus can generate spontaneous oscillations of 0.5–4 Hz even after severing its connections with the cortex, which suggests an important thalamic contribution in the genesis of delta waves.

In vitro experiments on thalamocortical (TC) cells have demonstrated an intrinsic low-threshold Ca\(^{2+}\) spike (Jahnsen and Llinas, 1984a) and a tendency to oscillate. Cat and rat TC neurons display spontaneous slow oscillations in the delta range (Haby et al., 1988; Leresche et al., 1990, 1991; McCormick and Pape, 1990a) which are resistant to tetrodotoxin and therefore due to mechanisms intrinsic to the cell. These slow oscillations have also been called “pacemaker oscillations” (Leresche et al., 1990, 1991).

A waxing and waning oscillation was also found in cat TC cells in vitro (Leresche et al., 1990, 1991). These oscillations are composed of periods of 1.5–28 s of 0.5–3.2-Hz oscillation that wax and wane, separated by silent phases of 5–25-s duration. They are resistant to tetrodotoxin and are caused by mechanisms intrinsic to the TC neuron. By analogy with the waxing and waning of in vivo spindles, they have been called “spindle-like oscillation” (Leresche et al., 1990, 1991). However in vivo spindles occur at a higher intrarust frequency (7–14 Hz) and depend on interactions with neurons of the thalamic reticular nucleus (Steriade and Deschenes, 1984; Steriade et al., 1985, 1987, 1990), so they are quite different from the waxing and waning slow oscillations studied here.

Electrophysiological investigations of the ionic mechanisms responsible for the intrinsic properties of TC neurons have revealed the presence of a low-threshold Ca\(^{2+}\) current, \(I_T\), responsible for the generation of low-threshold spikes (LTS) following hyperpolarization (Deschenes et al., 1984; Jahnsen and Llinas, 1984b). More recently, voltage-clamp studies of this current in TC cells (Coulter et al., 1989; Crunelli et al., 1989; Huguenard and Prince, 1992) characterized the kinetic properties of \(I_T\) and the characteristic activation of this current in the subthreshold region of the membrane potential.

A mixed Na\(^{+}/K\(^{+}\) current, \(I_h\), responsible for anomalous rectification, has also been identified in TC neurons studied in vitro (McCormick and Pape, 1990a; Pollard and Crunelli, 1988). The voltage-clamp technique has revealed that \(I_h\) is activated by hyperpolarization in the subthreshold range of potentials (McCormick and Pape, 1990a; Soltesz et al., 1991). This current was also shown to be involved in the generation of the slow oscillations of TC neurons (McCormick and Pape, 1990a; Soltesz et al., 1991) as well as in the state control of TC neurons by several neuromodulatory systems (McCormick and Pape, 1990a; McCormick and Williamson, 1991; Pape, 1992). The regulation of \(I_h\) can also control the transition between slow oscillations and waxing and waning oscillations in cat TC cells (Soltesz et al., 1991).

The purpose of the present paper is to investigate possible ionic mechanisms underlying the waxing and waning oscillations observed in single TC cells in vitro using a model of the TC neuron. The kinetic mechanisms in the model are...
based on voltage-clamp data of $I_T$ and $I_h$. Special emphasis is given to uncovering the role of $I_h$ 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:

$$\frac{dV}{dt} = \frac{g_m}{C_m}(V - E_m) - I_T - I_h - I_{k_2} + I_{ext},$$

(1)

where $C_m = 1 \mu F/cm^2$ is the specific capacity of the membrane, $g_m = 0.05$ mS/cm$^2$, and $E_k = -86$ mV are, respectively, the leakage conductance and the leakage reversal potential. The value of $g_m$ was chosen to obtain a membrane time constant of 20 ms, and $E_k$ was adjusted to match the resting membrane potential to -60 mV (Jahnsen and Linss, 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 $I_h$, and the voltage-dependent K$^+$ current $I_{k_2}$. $I_{k_2}$ represents the external current applied to the cell. Other Na$^+$ and K$^+$ currents, such as $I_{Na}$ and $I_K$, responsible for the generation of action potentials, $I_{Na}$, $I_{K_{Na}}$, or $I_{Kt}$ were not included in the model (for details on these currents see McCormick and Huguenard, 1992).

Kinetic models have been developed previously for $I_h$ (Huguenard and McCormick, 1992; Wang et al., 1991), for $I_{k_2}$ (Destexhe and Babloyantz, 1993; Huguenard and McCormick, 1992), and $I_T$ (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 kinetic equations read:

$$I_T = \frac{g_{Ca}m^3h(V - E_{Ca})}{h}$$

$$m = \frac{m_a(V)}{\tau_a(V)[m - m_a(V)]}$$

$$h = \alpha_h(V)[1 - h - d - K(V)h]$$

$$d = \alpha_d(V)[K(V)(1 - h - d) - d],$$

(2)

where $g_{Ca} = 1.75$ mS/cm$^2$ is the maximum value of the conductance of the Ca$^{2+}$ current and $E_{Ca}$ is the Ca$^{2+}$ reversal potential (in the presence of Ca$^{2+}$ diffusion, $E_{Ca}$ was calculated from the Nernst relation, and was taken as $E_{Ca} = 120$ mV otherwise). In this kinetic scheme, $m$ is the activation and $h$ and $d$ are two inactivation variables. The variable $d$ accounts for the slow recovery of $I_T$ from inactivation (Wang et al., 1991). The various functions used here are listed in Table 1.

The hyperpolarization activated current $I_h$

Voltage-clamp studies on thalamocortical neurons (McCormick and Pape, 1990a; Soltész et al., 1991) have shown that $I_h$ is a noninactivating current that activates slowly. This current is carried by both Na$^+$ and K$^+$ ions, and its reversal potential lies between $E_{Na}$ and $E_K$ (McCormick and Pape, 1990a). $I_h$ activates in the same subthreshold range of membrane potentials as $I_T$.

### Table 1: Activation functions and time constants for the voltage-dependent currents $I_T$, $I_h$, 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>$m_a(V)$</td>
<td>$m_a(V) = \frac{1}{1 + \exp\left(-\frac{V - 65}{7.8}\right)}$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_a(V)$</td>
<td>$\alpha_a(V) = \frac{1}{\tau_a(V)[1 + \exp(-13.5\tau_a(V))]}$</td>
</tr>
<tr>
<td></td>
<td>$K(V)$</td>
<td>$K(V) = \sqrt{\frac{0.25 + \exp\left(V + 85.5\right)}{0.63}} - 0.5$</td>
</tr>
<tr>
<td></td>
<td>$\tau_h(V)$</td>
<td>$\tau_h(V) = 62.4\tau_h(V)(1 + \exp\left(V + 39.4\right))$</td>
</tr>
<tr>
<td>$I_h$</td>
<td>$S_1(V)$</td>
<td>$S_1(V) = \exp\left(V + 183.6\right)\cdot 15.24$</td>
</tr>
<tr>
<td></td>
<td>$S_2(V)$</td>
<td>$S_2(V) = \exp\left(V - 1329\right)\cdot 200$</td>
</tr>
<tr>
<td></td>
<td>$S_3(V)$</td>
<td>$S_3(V) = \exp\left(V + 158.6\right)\cdot 11.2$</td>
</tr>
<tr>
<td></td>
<td>$S_4(V)$</td>
<td>$S_4(V) = \exp\left(V + 75.5\right)\cdot 5.5$</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 $g_{lo}$ values of 5 and 3 for $I_T$ (Coulter et al., 1989), and of 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 $I_h$ was introduced to account for the kinetic properties of $I_h$ (Destexhe and Babloyantz, 1993). Two distinct activation gates were assumed, namely $F$ (fast activation) and $S$ (slow activation) according to the following kinetic scheme:

$$S \rightarrow_{pS} S_{open} \quad F \rightarrow_{pF} F_{open}$$

where $S_{closed}$ and $F_{closed}$ represent the closed states of the slow and fast activation gates of $I_h$, $S_{open}$ and $F_{open}$ represent the open states of these gates, and $\alpha_S, \beta_S, \alpha_F$, and $\beta_F$ are voltage-dependent rate constants (see below).

The corresponding kinetic equations are:

$$I_h = \frac{g_hS_1F_1(V - E_h)}{h_b}$$

$$S_1 = \alpha_S(V)S_0 - \beta_S(V)S_1$$

$$F_1 = \alpha_F(V)F_0 - \beta_F(V)F_1,$$

(4)

where $g_h$ is the maximal conductance of $I_h$ (in mS/cm$^2$), $E_h = -43$ mV is the reversal potential of $I_h$ (McCormick and Pape, 1990a), $S_0 = 1 - S_1$, and $F_0 = 1 - F_1$. $S_0$ and $F_0$ represent the fraction of activation gates in the closed state, whereas $S_1$ and $F_1$ are the fraction of activation gates in the open state. The conductance of $I_h$ is always proportional to the product $S_1F_1$ in this model.

The rate constants are related to the activation function $H_a(V)$ and the time constants $\tau_a(V)$ and $\tau_p(V)$ by the following relations: $\alpha_S = H_a/\tau_a$, $\beta_S = (1 - H_a)/\tau_a$, $\alpha_F = H_p/\tau_p$, and $\beta_F = (1 - H_p)/\tau_p$. The activation function $H_a(V)$ was chosen so that $H'$ fits the data of McCormick and Pape (1990a) (see Table 1). The time constants $\tau_a(V)$ and $\tau_p(V)$ (given in Table 1) were estimated from numerical simulation of voltage-clamp protocols (see Results).

**Regulation of $I_h$ by intracellular Ca$^{2+}$**

Two plausible ionic mechanisms which produce waxing and waning oscillatory behavior are presented in Results. One possibility, initially pro-
posed by McCormick (1992), is the regulation of $I_b$ by binding of intracellular Ca$^{2+}$, as found in whole cell voltage-clamp studies of $I_b$ in sinoatrial node cells (Hagiwara and Irisawa, 1989). Evidence for the control of the voltage-dependent properties of $I_b$ by intracellular Ca$^{2+}$ were also obtained in cat neocortical neurons (Schwindt et al., 1992). As the Ca$^{2+}$ dependence of $I_b$ has not yet been studied in TC cells, it was assumed to be similar to that of sinoatrial node cells.

The activation curve of $I_b$ in sinoatrial node cells shifts toward more positive potentials as the intracellular Ca$^{2+}$ concentration ([Ca]) is increased (Hagiwara and Irisawa, 1989). Calmodulin and protein kinase C were not involved in the Ca$^{2+}$ modulation of $I_b$, suggesting that Ca$^{2+}$ ions directly affected $I_b$ channels (Hagiwara and Irisawa, 1989). There is also an increase in the conductance of $I_b$ following the binding of Ca$^{2+}$. We have developed a kinetic model for intracellular calcium (Ca$^{2+}$) binding to the open channels of $I_b$ that is consistent with these data. The open state gates $S_{open}$ and $F_{open}$ were assumed to have $n$ binding sites for Ca$^{2+}$ which, when occupied, lead to the open forms $S_{bound}$ and $F_{bound}$ according to:

$$S_{open} + nCa^{2+} \rightleftharpoons S_{bound}$$
$$F_{open} + nCa^{2+} \rightleftharpoons F_{bound}$$

where $k_1$ and $k_2$ are the forward and backward rate constants for Ca$^{2+}$ binding.

If $S_2$ and $F_2$ represent the fraction of gates bound to calcium, then, combining Eqs. 3 and 5, one obtains the following kinetic equations for $I_b$:

$$I_b = \delta_b(S_1 + S_2)(F_1 + F_2)(V - E_b)$$
$$S_1 = \alpha_b(V)S_0 - \beta_b(V)S_1 + k_1[S_2 - CS_1]$$
$$F_1 = \alpha_b(V)F_0 - \beta_b(V)F_1 + k_2[F_2 - CS_1]$$

where $S_0 = 1 - S_1 - S_2, F_0 = 1 - F_1 - F_2$, C = ([Ca]/[Ca_{crit}])$^n$, and $\alpha_b$, $\beta_b$, and $k_2$ were obtained from $H_b$ and $\tau_b$ as before. The number of binding sites was $n = 2$ in all of our simulations. We assumed $k_1 = k_2[Ca^{2+}] = 5 \times 10^{-4} \text{ mM}$ is the critical value of [Ca], at which Ca$^{2+}$ binding on $I_b$ channels is half-activated (if [Ca] $\ll$ [Ca_{crit} the effect of Ca$^{2+}$ is negligible; see Results for the estimation of this parameter from voltage-clamp data). $k_2 = 4 \times 10^{-4} \text{ ms}^{-1}$ is the inverse of the time constant of Ca$^{2+}$ binding on $I_b$ channels. These values were chosen to match the slow time course with which $I_b$ is modulated by intracellular Ca$^{2+}$.

**Influx and efflux of Ca$^{2+}$**

The dynamics of intracellular Ca$^{2+}$ were determined by two contributions:

(i) **Influx of Ca$^{2+}$ due to $I_T$**

Ca$^{2+}$ ions enter through $I_T$ channels and diffuse into the interior of the cell. Only the Ca$^{2+}$ concentration in a thin shell beneath the membrane was modeled. The influx of Ca$^{2+}$ into such a thin shell followed:

$$[Ca] = -\frac{k}{2Fd}I_T,$$

where $F = 96489 \text{ C mol}^{-1}$ is the Faraday constant, $d = 1 \mu\text{m}$ is the depth of the shell beneath the membrane, and the unit conversion constant is $k = 0.1$ for $I_T$ in $\mu\text{A/cm}^2$ and [Ca], in millimolar.

(ii) **Efflux of Ca$^{2+}$ due to an active pump**

In a thin shell beneath the membrane, Ca$^{2+}$ retrieval usually consists of a combination of several processes, such as binding to Ca$^{2+}$ buffers, calcium efflux due to Ca$^{2+}$ ATPase pump activity and diffusion to neighboring shells. Only the Ca$^{2+}$ pump was modeled here. We adopted the following kinetic scheme:

$$Ca^{2+} + P \rightleftharpoons CaP \rightarrow P + Ca^{2+},$$

where $P$ represents the Ca$^{2+}$ pump. CaP is an intermediate state, Ca$^{2+}$ is the extracellular Ca$^{2+}$ concentration, and $c_1, c_2, c_3$ are rate constants. Ca$^{2+}$ ions have a high affinity for the pump $P$, whereas extrusion of Ca$^{2+}$ follows a slower process (Blaustein, 1988). Therefore, $c_3$ is low compared to $c_1$ and $c_2$, and the Michaelis-Menten approximation can be used for describing the kinetics of the pump. According to such a scheme, the kinetic equation for the Ca$^{2+}$ pump is:

$$[Ca] = -\frac{K_f[Ca]}{[Ca] + K_i},$$

where $K_f = 10^{-4} \text{ mM ms}^{-1}$ is the product of $c_3$ with the total concentration of $P$, and $K_i = c_2/c_1 = 10^{-4} \text{ mM}$ is the dissociation constant, which can be interpreted here as the value of [Ca] at which the pump is half-activated (if [Ca] $\ll$ $K_i$ then the efflux is negligible).

The parameters of the pump were adjusted in order to have a fast Ca$^{2+}$ removal, based on an estimation made from the time course of the spike after hyperpolarization in TC cells (McCormick and Huguenard, 1992). Slow Ca$^{2+}$ handling is unlikely since Ca$^{2+}$-dependent channels would detect a slow Ca$^{2+}$ accumulation in TC cells.

The extracellular Ca$^{2+}$ concentration was [Ca]$_{ex} = 2$ mM as found in vivo. The change of [Ca] due to the binding of Ca$^{2+}$ to $I_b$ channels was negligible and was neglected, as was the contribution of Ca$^{2+}$ efflux to the net Ca$^{2+}$ current in Eq. 7.

The Ca$^{2+}$ reversal potential strongly depends on the intracellular Ca$^{2+}$ concentration, and was calculated according to the Nernst relation:

$$E_{Ca} = \frac{k'RT}{2F} \log \frac{[Ca]}{[Ca]_0},$$

where $R = 8.31 \text{ J mol}^{-1} \text{ K}^{-1}$, $T = 309^\circ \text{ K}$, and the constant for unit conversion is $k' = 1000$ for $E_{Ca}$ in mV. For [Ca]$_{ex} = 2.4 \times 10^{-4} \text{ mM}$, which is an average value at rest in the simulations presented here, $E_{Ca}$ was approximately 120 mV.

**Slow K$^+$ current $I_{K2}$**

A second plausible ionic mechanism for the generation of waxing and waning oscillations depends on the interaction between three ionic currents, namely $I_{K2}, I_{K3}$ and a slow outward current. Different types of K$^+$ currents have been recently identified in TC cells (Buddel et al., 1992; Huguenard and Prince, 1991; McCormick, 1991). Among these, a slowly inactivating K$^+$ current activated by depolarization was characterized and termed $I_{K2}$ by Huguenard and Prince (1991). They reported that this current inactivates very slowly with two time constants (around 250 ms and 3 s). A very similar current was found in TC cells in the lateral geniculate nucleus (McCormick, 1991). A kinetic model for this current was proposed by Huguenard and McCormick (1992):

$$I_{K2} = \delta_{K2}m_2(0.6h_1 + 0.4h_2)(V - E_K)$$

$$m_2 = -\frac{1}{\tau_{m2}(V)}(m_2 - m_{2\infty})$$

$$h_1 = -\frac{1}{\tau_{h1}(V)}(h_1 - h_{2\infty})$$

$$h_2 = -\frac{1}{\tau_{h2}(V)}(h_2 - h_{2\infty})$$

where $\delta_{K2}$ is the maximum value of $I_{K2}$ conductance and $E_K = -90$ mV is the reversal potential for K$^+$ ions. The activation function and the time constant of the activation variables $m_2$, $h_1$, and $h_2$ are given in Table 1.
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 $E_c$ is increased, $g_m$ must be decreased to reproduce similar results. We tested a broad range of maximal conductances and similar results were obtained.

Methods for solving the equations

Exploration of the behavior of the system over a large range of values of the parameters was performed using programs developed specifically for the purpose of this paper, or by using the NEURON simulator (Hines, 1989, 1993). The solutions were obtained by direct integration of the differential equations using a fifth order, variable-step integration subroutine, provided by the CERN library (MERSON D208: accuracy of $10^{-5}$-$10^{-6}$%, minimal step reached $10^{-1}$-$10^{-2}$ ms). These solutions were rigorously identical to those obtained from the NEURON simulator (Euler integration, minimal step of $10^{-1}$-$10^{-2}$ ms).

The stationary states of the system (see Results) were calculated analytically, and the equations obtained were solved numerically by using a Newton-Raphson algorithm (Press et al., 1986). A confirmation of the value of the stationary state was also provided by direct integration of the differential equations.

The programs written for the purpose of this paper and the NEURON simulator were run on UNIX workstations (SONY NWS 3410 and MIPS 3000), and the typical time taken by a simulation of 10 s was of the order of 8-16 s CPU time.

RESULTS

TC cells exhibit several types of slowly oscillating states in the subthreshold range of potentials ($-60$ to $-80$ mV). These oscillations were based on interactions between subthreshold currents, such as the low threshold Ca$^{2+}$ current $I_T$ and the hyperpolarization-activated current $I_{h}$. In particular, the mechanisms proposed here depend strongly on the kinetic properties of $I_{h}$. The parameters for $I_{h}$ in our model were adjusted to fit voltage-clamp data.

Ca$^{2+}$ and voltage-dependent activation of $I_h$

The activation function of $I_h$ at equilibrium as a function of the membrane potential and the intracellular Ca$^{2+}$ concentration is, from Eq. 6:

$$H_a(V, [Ca]_i) = [S_1 + S_2](F_1 + F_2)_{eq}$$

$$= \left[ \frac{1 + C}{H_a(V) - 1 + C} \right]^2,$$

where $C = ([Ca]/Ca_{eq})^n$, $H_a(V) = H_a(V, [Ca]_i = 0)$. The activation function $H_a(V, [Ca]_i)$ was determined from voltage-clamp measurements of TC neurons (McCormick and Pape, 1990a), and the parameters of $H_a(V)$ were chosen to fit as closely as possible these data (Fig. 1 B, solid line).

Whole cell voltage-clamp experiments (Hagiwara and Irisawa, 1989) on sino-atrial node cells have shown that increasing intracellular Ca$^{2+}$ produces a shift of the activation function of $I_h$ toward more positive membrane potentials. Using patch pipettes containing various concentrations in Ca$^{2+}$, the shift was around 13 mV for the highest concentrations in Ca$^{2+}$ used.

These data can be accounted for by a kinetic scheme where intracellular Ca$^{2+}$ directly binds to the $I_h$ channels (see Fig. 1 A and Materials and Methods). The activation function $H_a(V, [Ca]_i)$ progressively shifts toward positive membrane potentials as the value of $C$ increases (Fig. 1 B).

The shift at half-activation of $I_h$ is obtained by substituting $H_a(V, [Ca]_i) = 0.5$ into Eq. 12, to obtain:

$$V_{1/2} = -68.9 + 6.5\log(\sqrt{2} - 1) \log(C + 1) = -75 + 6.5 \log\left(\frac{[Ca]_i}{Ca_{eq}}\right)^n + 1.$$

FIGURE 1. Ca$^{2+}$-induced shift of the activation function of $I_h$. (A) Schematic diagram illustrating the currents in the model. The low-threshold Ca$^{2+}$ current ($I_h$) lets Ca$^{2+}$ ions enter the cell; these ions bind to the mixed Na$^+$/K$^+$ channel $I_h$ and modify its voltage-dependent properties. (B) Direct binding of intracellular Ca$^{2+}$ to $I_h$ channels shifts the voltage dependence of the current toward positive membrane potentials. $H_a(V, [Ca]_i)$ is represented as a function of the membrane potential $V$ for different values of $[Ca]_i$. The activation function at resting level of $[Ca]_i$ (solid line: $C = 0$) was estimated from voltage-clamp experiments (McCormick and Pape, 1990a) on TC cells (+ symbols). For increasing concentrations of intracellular Ca$^{2+}$, the activation function shows progressively larger shifts toward positive membrane potential (dashed lines, $C = 1$ and $C = 10$). $C = ([Ca]/Ca_{eq})^n$. 


The shift of the $I_h$ activation logarithmic in $[\text{Ca}]$, and a shift of 13 mV is obtained for $C = 6.4$.

The shift should be negligible ($C < 1$) at the resting level, $[\text{Ca}]$, $\sim 2 \times 10^{-4}$ mM, which gives a lower bound: $C_{\text{crit}} > 2 \times 10^{-4}$ mM. During activation of $I_T$, the value of $[\text{Ca}]$, 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: $C_{\text{crit}} < 10^{-2}-10^{-3}$ mM. In the simulations presented here, we chose $n = 2$ and $C_{\text{crit}} = 5 \times 10^{-4}$ 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; Soltész 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 very 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 $S_1F_1$, 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 $\text{Ca}^{2+}$ is introduced and its interactions with other currents examined.

**Oscillatory behavior from $\text{Ca}^{2+}$-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 Sejnowski, 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 $\text{Ca}^{2+}$.

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 $g_h$ ($< 0.01 \text{mS/cm}^2$), 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; Soltész et al., 1991) after blockade of $I_h$.

For the highest values of this conductance ($g_h > 0.1 \text{mS/cm}^2$), 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; Soltész 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/cm$^2$, 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/cm$^2$), 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 $\text{Ca}^{2+}$-dependent waxing and waning oscillations**

Soltész et al. (1991) showed that slow oscillations and waxing and waning oscillations observed in cat TC cells are two
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 \( \bar{g}_h \). For some values of \( \bar{g}_h \), 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. 4 B). During the burst there was a gradual depolarization that was most clearly seen by averaging the membrane potential (Fig. 4 C).

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, \( Ca^{2+} \) entered transiently at the peak of each spike and bound progressively to \( I_h \) channels (reflected in the slow increase of \( S_2 \) and \( F_2 \). \( Ca^{2+} \) binding to \( I_h \) channels shifted the \( I_h \) activation curve, producing a gradual depolarization during the oscillatory phase (Fig. 4 C). 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 \( g_h = 0.02 \text{ mS/cm}^2 \) from slow oscillations to a state where the slow oscillations were interrupted by short silent phases (Fig. 6 B). As \( g_h \) 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 \( g_h \) are reported in Fig. 7 A. The silent phase ranged from 4 to 20 s and decreased with \( g_h \). The oscillatory phase became shorter with increase of \( g_h \). In the limit, as \( g_h \) decreased to 0.02 mS/cm\(^2\), the duration of oscillatory phase tended to infinity. The opposite occurred 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 \( g_h \) before the depolarized state appeared). The period of the slow oscillation decreased with \( g_h \) (indicated by \( S \) in Fig. 7 A), which is consistent with the slowing down of the slow oscillation observed after progressive blockage of \( I_h \) channels by cesium (McCormick and Pape, 1990a).

The length of the silent phase and of the oscillatory phase were directly proportional to the time constant of intracellular \( \text{Ca}^{2+} \) binding to \( I_h \) channels, \( k_{-1} \) (Fig. 7 B). This is

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**FIGURE 3** Resting states and slow oscillations in the presence of \( I_r \) and \( \text{Ca}^{2+} \)-dependent \( I_h \) obtained at four values of the maximal conductance of \( I_h \). (A) Hyperpolarized resting state close to \(-84 \text{ mV} \) for \( g_h = 0 \). (B) Slow oscillations of about 3.5 Hz for \( g_h = 0.01 \text{ mS/cm}^2 \). (C) Waxing and waning oscillations of about 4–8 Hz for \( g_h = 0.04 \text{ mS/cm}^2 \). (D) Depolarized resting state around \(-58 \text{ mV} \) for \( g_h = 0.11 \text{ mS/cm}^2 \). The maximum conductance of \( I_r \) was kept fixed at \( g_{Ca} = 1.75 \text{ mS/cm}^2 \).

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**FIGURE 4** Properties of \( \text{Ca}^{2+} \)-dependent waxing and waning oscillations. (A) Transformation of waxing and waning oscillations into slow oscillations by application of a depolarizing current step of 0.05 \( \mu \text{A/cm}^2 \) (arrow). \( g_h = 0.04 \text{ mS/cm}^2 \). (B) Waxing and waning oscillations at high amplification showing the slow hyperpolarization of the membrane during the silent phase. \( g_h = 0.04 \text{ mS/cm}^2 \). (C) Average membrane potential showing a progressive depolarization during the oscillatory phase. Each point was obtained by averaging the membrane potential over a period of 500 ms. \( g_h = 0.025 \text{ mS/cm}^2 \).
consistent with the assumption that the binding of 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 \(k_2^{-1}\). 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 Ca\(^{2+}\)-dependent regulation of \(I_h\) is not the only way to obtain waxing and waning oscillation with \(I_T\) and \(I_n\). A second possible mechanism depends on the interaction among \(I_T\), \(I_h\), and the slow K\(^+\) current \(I_{K2}\). Ca\(^{2+}\) mechanisms were not included in this version of the model.

It was reported previously (Destexhe and Babiloyantz, 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 in 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 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 \(I_n\). Similar oscillations were observed when \(I_{K2}\) was replaced by slow K\(^+\) currents, such as the slow Ca\(^{2+}\)-activated K\(^+\) current or a depolarization-activated noninactivating 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 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
that wax and wane, usually result from several oscillatory or stationary states. In this section, the dynamical states underlying waxing and waning oscillations are studied using a singular approximation method that identifies the origin and the transitions between these states.

Singular approximation is used in nonlinear dynamics to separate fast and slow subsystems (Pontryagin, 1961; Zeeman, 1973). Slow variables can be treated as slowly varying parameters and the rest of the system can then be studied as a function of these new parameters. This approximation has been successfully used to uncover the dynamical mechanisms underlying bursting oscillations in models of several biological systems (Rinzel, 1987).

We have applied this method to our model of waxing and waning oscillations. In Fig. 5, the gating variables $S_2$ and $F_2$ evolved according to a slower time scale than the other variables. In the case of $I_{Kc2}$-dependent waxing and waning oscillations (Fig. 9), $S_1$ and $h_2$ were the slow variables.

Let $S_2$ be a slowly varying parameter in the Ca$^{2+}$-dependent model. In contrast, $F_2$ only displays small variations of amplitude and therefore has a less prominent role than $S_2$. As before, Eq. 6 was used for Ca$^{2+}$-dependent waxing and waning oscillations, except that $S_2$ was assigned a constant value. In Fig. 5 A, since the variable $S_2$ oscillates approximately between 0.09 and 0.65, the same interval of values will be used for $S_2$ treated as a parameter.

Over this range of values, the system showed either a stable resting state or limit cycle oscillations (Fig. 10 A). For the smallest values of $S_2$, the system exhibited slow oscillations at a frequency of about 3.5 Hz, whereas for the highest values of the parameter $S_2$, the system exhibited a stable stationary state close to the depolarized resting state of Fig. 3 (around −57 mV).

The transition point between limit cycle oscillations and stable stationary state is called a Hopf bifurcation (Guckenheimer and Holmes, 1986; Rinzel and Ermentrout, 1989). In some cases, the stable solutions overlap, and the bifurcation is called subcritical. In our system, this transition has the typical structure of a subcritical Hopf bifurcation. First, the amplitude of the limit cycle at the bifurcation point changed abruptly and there was no decline in amplitude. Second, in some range of values of the parameter $S_2$ (about 0.225–0.42),

FIGURE 6 Transformation from slow oscillations to waxing and waning oscillations. The pattern of oscillations is shown for four values of $g_h$. (A) slow oscillations ($g_h = 0.02$ mS/cm$^2$). (B) A short silent phase interrupted the slow oscillation ($g_h = 0.021$ mS/cm$^2$). (C) Oscillations with a longer silent phase ($g_h = 0.025$ mS/cm$^2$). (D) For larger values of $g_h$, the silent phase became more prominent ($g_h = 0.05$ mS/cm$^2$).
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.

Thus, in a waxing and waning sequence, $S_2$ oscillates between values which drive the system alternately between stable stationary states and slow oscillations. As shown by Fig. 10 B, the waxing and waning oscillations are driven around a hysteresis loop by the slow oscillations of $S_2$, as depicted by dotted arrows: as $S_2$ decreases during the silent phase, the membrane potential hyperpolarizes slowly and follows the stable stationary state branch (arrow 1). As the critical point is reached, the stationary state loses its stability and the system jumps to the oscillating branch (arrow 2). $S_2$ then starts to increase and follows the oscillating branch, while the amplitude of the oscillations decreases (arrow 3). The limit cycle oscillations lose stability and the system jumps back to the stationary branch (arrow 4). The oscillations damp and the silent phase starts again.

The trajectory of a simulated waxing and waning oscillation plotted in a V/S$_2$ diagram, shown in Fig. 10 D, alternates between an oscillating and a stationary branch in a manner very similar to that in Fig. 10 B. The position of the oscillating and stationary branches seems to be slightly different from the solutions displayed in Fig. 10 B, but the structure remains the same. Waxing and waning oscillations with a longer oscillatory phase (see Fig. 6) correspond to a very similar trajectory, with an increased number of loops near the end of the oscillatory branch.

The same subcritical Hopf structure is still present for slow oscillations, but the successive loops do not leave the oscillatory branch and the oscillation does not wax and wane. A strong current pulse should, however, be able to make the trajectory jump from the oscillatory branch to the stationary branch. This prediction is borne out in Fig. 11, where a strong depolarizing current step induced a sudden transition to a silent phase during the slow oscillation (indicated by arrows 2 and 3 in Fig. 11 B) and the system returned back to the oscillatory branch (arrow 4) along a single hysteresis loop. Steps applied to $S_2$ resulted in the same type of behavior.
The same analysis can be applied to the $I_{K2}$-dependent waxing and waning oscillations, using $S_1$ as a parameter. The $I_{K2}$-dependent waxing and waning oscillations were also based on a hysteresis loop around a subcritical Hopf bifurcation (not shown). The trajectory in the $V/S_2$ diagram was very similar to the $Ca^{2+}$-dependent waxing and waning oscillations (Fig. 12).

**DISCUSSION**

Hodgkin-Huxley-type models of TC neurons were first introduced by McMullen and Ly (1988) and Rose and Hindmarsh (1989) based on the experiments of Jahnse and Llinas (1984a). More recent models of TC neurons (Destexhe and Babloyantz, 1993; Lytton and Sejnowski, 1992; McCormick and Huguenard, 1992; Toth and Crunelli, 1992a) take into account data from voltage-clamp experiments. We have extended these models by incorporating a more accurate model of $I_h$ and have used it to study the genesis of waxing and waning oscillations that have been described in vitro (Leresche et al., 1990, 1991; Soltesz et al., 1991).

**The properties of $I_h$ in voltage-clamp mode**

The hyperpolarization-activated inward current $I_h$ is central to the oscillatory properties of TC neurons (McCormick and Pape, 1990a; Soltesz et al., 1991). First-order kinetic schemes have been proposed for modeling $I_h$ in TC cells (Huguenard and McCormick, 1992; Lytton and Sejnowski, 1992; Toth and Crunelli, 1992a), sino-atrial node cells (DiFrancesco and Noble, 1985; van Ginneken and Giles, 1991) and stomatogastric ganglion neurons (Buchholtz et al., 1992); however, they do not reproduce the slow component of activation and the difference between activation and deactivation kinetics.

The model of $I_h$ adopted here (Destexhe and Babloyantz, 1993) has two activation variables with different kinetics and accurately accounts for all the voltage-clamp data. Although more complex models have been developed for modeling a current similar to $I_h$ in sino-atrial cells (DiFrancesco, 1985), the model used here is relatively simple and explains how slow activation can coexist with faster deactivation.

A $Ca^{2+}$ dependence of $I_h$ was included based on voltage-clamp measurements on sino-atrial node cells (Hagiwara and
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\(^{2+}\) dependence of \(I_h\) is caused by direct binding of Ca\(^{2+}\) ions on the open form of \(I_h\) channels (for a different model of this shift in the context of TC cells, see Toth and Crunelli (1992b)). Our model accounts for the positive shift of the activation function of \(I_h\) with increased intracellular Ca\(^{2+}\), but not for the substantial increase of conductance. It should be possible to verify the predicted logarithmic shift (Eq. 12) from whole cell patch-clamp experiments.

**Combinations of currents giving rise to waxing and waning oscillations**

The properties of waxing and waning oscillations (Leresche et al., 1991) were reproduced by our model, which included \(I_T\) and Ca\(^{2+}\)-dependent \(I_h\). The silent phase was many seconds long, during which the membrane potential slowly hyperpolarized. A transition to periodic oscillations could be elicited by application of a depolarizing current step only for some values of the parameter \(g_{K2}\). Experimental studies report this transition in only two out of 39 cat TC cells (Leresche et al., 1991).

More importantly, the sequence of resting and oscillatory behavior obtained was identical to that determined in vitro (Soltész et al., 1991). In these experiments, noradrenaline (NE) was used to change \(I_h\), but NE also shifts the activation 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 there were long oscillatory phases and short silent phases. TC cells in vitro show a variety of patterns of waxing and waning oscillations with silent and oscillatory phases of different lengths. The range of patterns found in the model for different values of the parameters suggests that the variability observed in vitro might arise from a heterogeneity of the conductance values among neurons.

We also investigated the occurrence of waxing and waning oscillations in a model comprising \(I_T\), \(I_h\), and the slow K\(^+\) current \(I_{K2}\) (Destexhe and Babiloyantz, 1993). The main difference was that the frequency inside the oscillatory phase was significantly higher in \(I_{K2}\)-dependent waxing and waning oscillations (10–14 Hz) compared to the same oscillations obtained from the Ca\(^{2+}\)-dependent mechanism (3.5–4 Hz). The frequency of oscillations in the Ca\(^{2+}\)-dependent model was much closer to the experimental data of Leresche et al. (1991).

In the case of the Ca\(^{2+}\)-dependent model, the waxing and waning oscillations were modulated by the kinetics of binding of Ca\(^{2+}\), whereas, in the case of the \(I_{K2}\)-dependent model, they appear to be modulated by the slow activation of \(I_h\). Although the values of \(I_T\) and leakage parameters were the same, 10-fold higher values of \(g_{K2}\) were needed to observe similar types of behavior for the \(I_{K2}\)-dependent model.
Ca\(^{2+}\)-dependent waxing and waning oscillations were also observed in the presence of fast Na\(^+\) and K\(^+\) currents responsible for action potentials (unpublished; kinetics taken from Traub and Miles (1991)). In this case, waxing and waning oscillations occurred as sequences of rhythmic bursting (3.5–4 Hz; fast spikes at 50–300 Hz) separated by long silent phases (4–30 s).

**Dynamical mechanisms of waxing and waning oscillations**

Singular approximation was used to characterize the waxing and waning oscillation as an alternation between two dynamical states, a hyperpolarizing stationary phase and an oscillating phase. The transitions between these two states were made via a subcritical Hopf bifurcation. It was remarkable that the same dynamical mechanism underlies both the Ca\(^{2+}\)-dependent and the IK\(_2\)-dependent models, despite the different ionic mechanisms.

A similar type of dynamical mechanism was proposed previously by Rinzel (1987) for the Fitzhugh-Nagumo equations (Fitzhugh, 1961), in which a subcritical Hopf bifurcation emerged from a stationary state, leading to bursting oscillations. The same subcritical Hopf structure was also present during slow oscillations. We found that a strong depolarizing current pulse of 200 ms can force the TC cell out of the oscillatory phase for a period of about 15 s before the cells revert back to slow oscillations. However, weaker current pulses do not produce such an interruption but only affect the phase of the slow oscillations (not shown). This prediction of the model could be tested experimentally.

**The role of I\(_h\)**

Soltesz et al. (1991) suggested that slow oscillations and waxing and waning rhythmicity observed in vitro correspond to two different equilibria between I\(_T\) and I\(_h\). The results presented here are consistent with this hypothesis.

The pattern of oscillations depended on the value of the maximal conductance of I\(_h\) and slowly varying this parameter smoothly transforms the slow oscillations into waxing and waning oscillations. This suggests that slow oscillations and waxing and waning oscillations are part of a continuum of oscillating states that can be determined in part by the maximal conductance of I\(_h\).

The Ca\(^{2+}\)-dependent waxing and waning oscillations were insensitive to the details of the kinetics of the models for I\(_T\) and for the kinetics of binding of intracellular Ca\(^{2+}\) on I\(_h\) channels. However, when Ca\(^{2+}\) binding to I\(_h\) was modeled by a simple activation scheme (Huguenard and McCormick, 1992) rather than the double activation model (Destexhe and Babloyantz, 1993), then waxing and waning oscillations were not observed over a wide range of parameter values. These results suggest that the description of I\(_h\) by double activation kinetics might be important for robustly generating waxing and waning patterns of oscillation, but more evidence is needed to demonstrate this point.

**Implications for the physiology of thalamic oscillations**

Our model suggests that interactions between I\(_T\), I\(_h\), and the leakage currents are the kernel that allows the coexistence of
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 \(I_{K_2}\)-dependent model makes it less plausible than the \(Ca^{2+}\)-dependent model. The \(I_{K_2}\)-dependent model predicts that the waxing and waning oscillations should not survive blockage of all voltage-dependent K\(^+\) currents (but not the leak K\(^+\) currents, needed to maintain the level of membrane potential). The \(Ca^{2+}\)-dependent model could be tested by altering the intracellular \(Ca^{2+}\) levels while monitoring the period of waxing and waning oscillations. The \(Ca^{2+}\)-dependent model predicts that this period should be sensitive to intracellular \(Ca^{2+}\).

The intrinsic oscillating properties of TC cells are difficult to reconcile with the various types of oscillations found in vivo (Nunez et al., 1992). The occurrence of spindling in vivo is thought to be a combination of intrinsic and network properties (Steriade and Llinares, 1988; Steriade et al., 1993b). In particular, single thalamic reticular cells are characterized by 7–12-Hz intrinsic oscillations (Avanzini et al., 1989; Bal and McCormick, 1993), close to the typical frequency of sleep spindles. Spindle rhythmicity was also found in the isolated reticular thalamus in vivo (Steriade et al., 1987). On the other hand, TC cells have a clear tendency to oscillate at a lower frequency of 0.5–4 Hz (Curró Dossi et al., 1992; Lerescu et al., 1990, 1991; McCormick and Pape, 1990a) and have been shown to have an active role in the generation of spindles in vitro (von Krosigk et al., 1993). Computer models of the intrinsic oscillatory properties of thalamic reticular and TC cells, as well as their pattern of connectivity, could help us to understand the cellular bases of spindling (Destexhe et al., 1993a,b).

We thank Drs. Diego Contreras, John Huguenard, William Lytton, David McCormick and Mircea Steriade for stimulating discussions.

This research was supported by the Belgian government (ARC and IMPULS, project RFO AI 10), the European Community (ESPRIT, Basic Research, project 3234), the Howard Hughes Medical Institute, and the United States Office of Naval Research.

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