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 ($I_n$). $I_n$ 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 $I_n$, terminating the oscillations. A similar type of waxing and waning oscillation was also observed, in the absence of Ca$^{2+}$ regulation of $I_n$, from the combination of $I_T$, $I_n$, and a slow K$^+$ current. Singular approximation showed that for both models, the activation variables of $I_n$ controlled the dynamics of thalamocortical cells. Dynamical analysis of the system in a phase plane diagram showed that waxing and waning oscillations arose when $I_n$ 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 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 (Curro 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).

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 intraburst 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, $I_n$, 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
based on voltage-clamp data of $I_T$ and $I_K$. 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.

**TABLE 1** Activation functions and time constants for the voltage-dependent currents $I_T$, $I_h$, and $I_K$.

<table>
<thead>
<tr>
<th>Current Variable</th>
<th>Function</th>
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<tbody>
<tr>
<td>$I_T$</td>
<td>$\text{activating function}$</td>
</tr>
<tr>
<td>$I_h$</td>
<td>$\text{inactivating function}$</td>
</tr>
<tr>
<td>$I_K$</td>
<td>$\text{inactivating function}$</td>
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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 positive potentials as the intracellular \( \text{Ca}^{2+} \) concentration ([Ca]_i) is increased (Hagiwara and Irisawa, 1989). Calmodulin and protein kinase C cell flux due to \( \text{Ca}^{2+} \)-ATPase pump activity and diffusion to neighboring shells. Only the \( \text{Ca}^{2+} \) pump was modeled here. We adopted the following kinetic scheme:

\[
\text{Ca}^{2+}_i + P \rightleftharpoons \text{CaP} \rightleftharpoons P + \text{Ca}^{2+}_i, \tag{8}
\]

where \( P \) represents the \( \text{Ca}^{2+} \) pump, \( \text{CaP} \) is an intermediate state, \( \text{Ca}^{2+}_i \) is the extracellular \( \text{Ca}^{2+} \) concentration, and \( \epsilon_1, \epsilon_2, \text{and } \epsilon_3 \) are rate constants. \( \text{Ca}^{2+} \) ions have a high affinity for the pump \( P \), whereas extrusion of \( \text{Ca}^{2+} \) follows a slower process (Hagiwara, 1988).
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, $g_c$ must be decreased to reproduce similar behavior.
The shift of the $I_h$ activation logarithmic in $[\text{Ca}]_i$ and a shift of 13 mV is obtained for $C = 6.4$.

The shift should be negligible ($C < 1$) at the resting level, $[\text{Ca}]_i \sim 2 \times 10^{-3}$ mM, which gives a lower bound: $C_{\text{crit}} > 2 \times 10^{-4}$ mM. During activation of $I_h$, the value of $[\text{Ca}]_i$ 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.

$\tau_f(V)$, 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 (1993a) (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.
FIGURE 2  Activation and deactivation kinetics of $I_h$. (A) Simulation of voltage-clamp protocols of activation of $I_h$. (a) From an initial holding value of $-55$ mV, the voltage was clamped at various levels (from $-105$ to $-70$ mV) for 4 s, then clamped again to $-55$ mV. (b) Time course of the current compared to the voltage. (C) Membrane potential (initial voltage of 0 mV) vs. time constant of activation ($\tau_A$).
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 oscillator phase decreased 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 phase.
consistent with the assumption that the binding of Ca$^{2+}$ is critical for the onset and termination of the oscillatory phase during each cycle of the oscillatory phase. The resulting depolarization inactivates $I_n$ and the oscillations damp.

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 $S_3$ and $F_3$, is also expected to be propor
tional to the rate of $S_3$ and $F_3$.

Compared with the Ca$^{2+}$-dependent waxing and waning oscillations, the slow depolarization of the membrane during the oscillatory phase in the $I_{K_v}$-dependent model is provided by a more pronounced $I_n$ activation ($S_n$ reaches...
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 struc-
The same analysis can be applied to the $I_{K_2}$-dependent waxing and waning oscillations, using $S_1$ as a parameter. The $I_{K_2}$-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\textsuperscript{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 Jahnson and Llinas (1984a). More recent models of TC neurons (Destexhe and Babilonyantz, 1993; Lytton and Sejnowski, 1992; McCormick and Huguenard, 1992; Toth and Cruelli, 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 Cruelli, 1992a), sino-atrial node cells (DiFrancesco and Noble, 1985; vanGinneken 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 Babilonyantz, 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\textsuperscript{2+} dependence of $I_h$ was included based on voltage-clamp measurements on sino-atrial node cells (Hagiwara and
A. Slow oscillations ($S_2=0.09$)

B. Resting state ($S_2=0.65$)

C. 2 s

D. Potential (mV)
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 reverts back to slow oscillations. However, weaker current pulses do not produce such an interruption but only affect the...
tonic firing, slow oscillations, and waxing and waning os-


