Low Threshold Spikes and Rhythmic Oscillations in Thalamic Neurons

Xiao-Jing Wang[†], John Rinzel[†] and Michael A. Rogawski[‡]
[†]Mathematical Research Branch, NIDDK, Bldg. 31, Rm. 4B-54
and [‡]Medical Neurology Branch, NINDS, Bldg. 10, Rm. 5N-248
National Institutes of Health, Bethesda, Maryland 20892,USA

1 Introduction

The electrophysiological activity of thalamic relay neurons is critically dependent upon behavioral state. During drowsiness and quiet sleep (and possibly also during petit mal seizures), the cells may no longer be free to faithfully relay impinging synaptic input to the neocortex. Instead, they are intermittently constrained to fire bursts of action potentials in a synchronized, rhythmic fashion. Underlying these bursts is a slow membrane potential oscillation with a frequency of 7-14 Hz (but which may be slower during seizures). Whereas the hyperpolarizing phase of the cycle is mediated synaptically, possibly by the inhibitory drive of cells in the nucleus reticularis thalami (RE), endogenous properties of the relay neurons themselves are largely responsible for the depolarizing part of the oscillation [6]. Thus, a Ca^{2+}-dependent depolarizing event or "low threshold spike" (LTS) is triggered as the synaptic inhibition decays and the LTS, in turn, evokes a burst of Na^{+}-dependent action potentials that ride upon its peak. Experimental evidence has recently implicated T-type (low threshold) voltage-dependent Ca^{2+} channels as mediators of the LTS [7]. In what follows we summarize our theoretical work supporting a critical role of the T-type Ca^{2+} channel in the generation of the LTS. Moreover, we investigate possible mechanisms responsible for the rhythmic firing of RE neurons. Like relay neurons, RE cells also exhibit LTS and bursting behavior [2], although voltage clamp data for these cells are not yet available. We have found that a minimal model of two cells that possess T-type Ca^{2+} channels and interact with each other via synaptic inhibition is able to generate rhythmic oscillations at an appropriate frequency (about 10 Hz). We show that the oscillatory period can be modulated by both intrinsic cellular properties (kinetics of the T-type Ca^{2+} channels), *and* the characteristics of the synaptic inhibition between cells.

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2 A Quantitative Model of the Low Threshold Spike

Recent voltage clamp recordings from enzymatically isolated thalamic relay neurons [1] have provided data which allow a detailed model of the T-type Ca^{2+} current in these cells to be elaborated. This current I_T can be written in a Hodgkin-Huxley format as $I_T = \bar{g}_{Ca} m^3 h (V - V_{Ca})$. Here, m and h are the activation and inactivation variables. Their steady state values $m_\infty(V)$ and $h_\infty(V)$ are sigmoid functions of the membrane potential V; m_∞ and $(1 - h_\infty)$ tend to 0 and 1 as $V \to -\infty$ and $+\infty$, respectively. With midpoints at $\theta_m = -63$ mV and $\theta_h = -83.5$ mV, respectively, the two curves hardly overlap. Since θ_h is significantly more negative than the resting membrane potential (~ -60 mV), I_T can be elicited only by hyperpolarization from the resting state, such as is produced by inhibitory synaptic input.

The prolonged recovery time of I_T has suggested to us that the *dynamics* of the inactivation gate are complex. Unlike the activation gates which are governed by first order kinetics with a single time constant $\tau_m(V)$, the inactivation gate appears to require a kinetic scheme with at least two transition steps, the first between an open state O and a closed state C_1, and the second between C_1 and another (deep) closed state C_2. We denote the time constants for the transition step between O and C_1 and between C_1 and C_2, as $\tau_1(V)$ and $\tau_2(V)$, respectively. τ_1 determines the speed of the inactivation process of the T-type current, while τ_2 controls its slow recovery. Based on recent whole-cell voltage clamp data [1], we have constructed analytical expressions for τ_m, τ_1 and τ_2 as functions of the membrane potential V. At $37°C$, and within the voltage range at which I_T can be activated (~ -60 to -90 mV), $\tau_m \sim 1.5$ ms, $\tau_1 \sim 15$ ms and $\tau_2 \sim 70 - 90$ ms.

Our model of the T-type Ca^{2+} channel has been tested in various voltage clamp simulations and has been found to reproduce well available experimental observations. To simulate current clamp conditions, we added a leakage current, $I_L = \bar{g}_L (V - V_L)$, and showed that this two-current model (see Appendix) suffices to describe basic features of the LTS. In these computations, a slow transient depolarization can be elicited upon release from a hyperpolarizing applied current. Moreover, because of the slow time scale of the deinactivation process, the applied current must be maintained for a prolonged period of time in order to obtain a well developed LTS.

A two-pulse protocol illustrates well this characteristic of the T-type Ca^{2+} current (cf. Fig.1). The membrane potential is maintained at a negative value of about $V = -85$ mV by a constant hyperpolarizing current. At this voltage the activation gates are almost totally closed ($m \simeq 0$), hence $I_T \simeq 0$, while the inactivation gates populate primarily the open state O so that h is substantially greater than 0. When a depolarizing pulse is applied, the membrane potential starts to rise. Because of the disparate time scales, m increases much more rapidly than h decreases, resulting in a transient depolarizing spike. The termination of the spike is due to the inactivation of I_T, i.e., at depolarizing po-

tentials most of the inactivation gates tend to the deep closed state C_2 ($h \simeq 0$), hence $I_T \simeq 0$. After the first pulse the cell is again hyperpolarized to -85 mV, and the T-type channel starts to *deinactivate*, i.e., there is a transition flux from the deep closed state C_2 to C_1, then to O. Since the first transition step is much slower than the second, the outlet from the deep closed state serves as a "bottleneck" in the deinactivation process. Therefore, if a second depolarizing current pulse is to generate a second LTS of size comparable to the first, the duration of the interpulse hyperpolarization must exceed the time constant τ_2 of the transition process between C_2 and C_1 (about 90 ms at -85 mV).

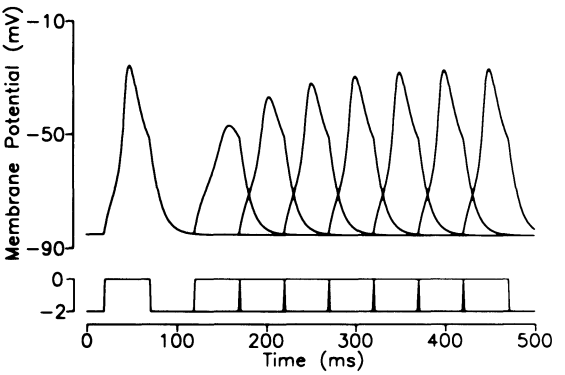

Fig.1. Release from a holding hyperpolarizing current produces an initial low threshold spike (LTS). A second release pulse of 50 ms is applied at increasing latencies. Near full recovery appears after a refractory time of about 100 ms. The unit of applied current is $\mu A/cm^2$. See Appendix for parameter values.

Consequently, and this is a main point we wish to emphasize, the time scale of the "bottleneck effect" of the I_T-deinactivation process imposes a severe upper limit on the frequency of repetitive hyperpolarizations which can elicit a train of LTSs.

3 Oscillations in Two Cells Coupled by Synaptic Inhibition

An earlier modeling study [3] showed that reciprocal inhibition between cells with rebound excitation can lead to rhythmic behavior. Indeed, this mechanism is realized by two cells endowed with the T-type calcium current. Thus, during an LTS the depolarized cell (#1) would send inhibition to the other cell (#2), so that its T-current is deinactivated. At the end of the LTS of cell #1, cell #2 will be released from hyperpolarization, produce an LTS of its own and inhibit cell #1 in turn. In this way an out-of-phase oscillation may be triggered.

This mechanism appears of interest in connection with rhythmic activity in the nucleus reticularis thalami. There are some experimental data which show that the *isolated* nucleus reticularis can generate spindling oscillations, i.e., epoches of 10 Hz bursting oscillations [5]. The nucleus reticularis is believed to consist of a homogeneous population of cells, all of which possess the T-type Ca^{2+} current, and interact with each other through inhibitory, GABAergic synapses. The diffused projections from the nucleus reticularis to specific relay nuclei indicate a role for this particular thalamic nucleus as a pacemaker or "synchronizer" of the 10 Hz thalamic rhythmic activities.

Our simple two-cell model consists of identical cells, each of which has a T-type Ca^{2+} current and a leakage current, as in Section 2. Since our focus of attention is on the slow wave related to the LTS, we exclude in this model the Na^+ and K^+ currents responsible for the action potentials, and the A-type transient K^+ current (for a different model of a thalamic neuron with these currents, see [4]). A cell receives an inhibitory input from its partner if the latter is depolarized beyond a certain threshold θ_{syn}. The synaptic coupling is assumed to be instantaneous (a small delay would be negligible compared to the time span of an LTS). More precisely, a cell, say #1, receives a synaptic current from cell #2 of the form $I_{syn} = \bar{g}_{syn} S(V_2)(V_1 - V_{syn})$, where $S(V) = 1/(1+\exp(-(V-\theta_{syn})/k_{syn}))$ is a sigmoid function. Similarly for the synaptic current from cell #1 to cell #2. When this model is implemented numerically, an out-of-phase oscillation is indeed seen as the natural dynamic state of the system (cf Fig.2).

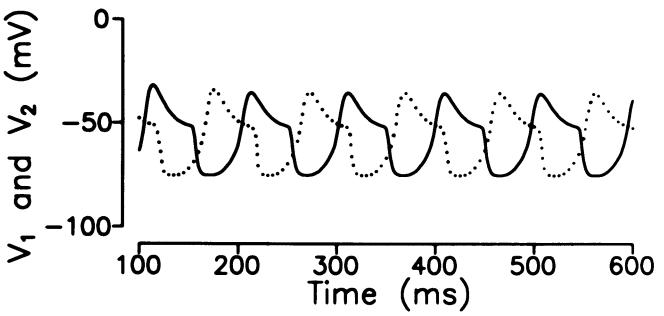

Fig.2. Out-of phase oscillation for two mutually inhibitory model neurons. Switching occurs when the membrane potential of the depolarized cell (#1) falls below θ_{syn}, thereby "releasing" cell #2 from inhibition; cell #2 then depolarizes with an LTS and inhibits cell #1. Parameter values in Appendix.

The oscillatory period P is dependent on two key parameters of our system: the recovery time τ_2 of I_T and the presynaptic voltage threshold θ_{syn} for activating the postsynaptic conductance (cf. Fig.3). As is already evident from Section 2, τ_2 sets a lower bound on the period of oscillation, and if it was

increased or decreased by a certain factor, all the other parameters being fixed, one would expect that the period of the oscillation will be also be changed in the same direction and with near proportionality. As for θ_{syn}, it controls the fraction of the LTS duration over which a depolarized cell sends effective inhibition to its target cell. Within a certain range, therefore, the more negative is θ_{syn}, the longer will be the inhibitory phase of oscillation, so also its period. This means that the period of such LTS-mediated oscillations in coupled cells would depend largely on the duration of the inhibitory postsynaptic conductance in these cells.

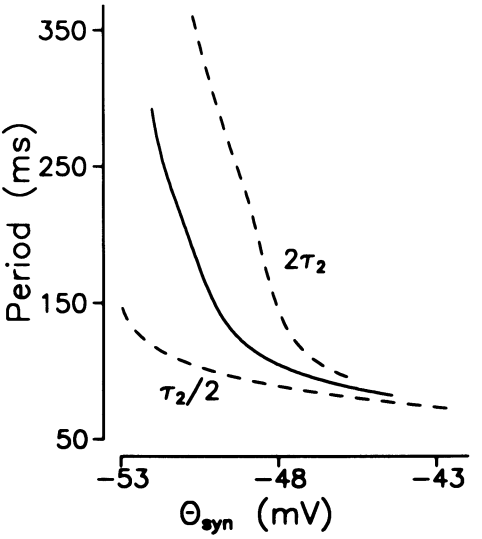

Fig.3. Oscillation period P versus θ_{syn}. Oscillation occurs only in an appropriate range of θ_{syn}. If θ_{syn} is too high, inhibition will be present too briefly to deinactivate the I_T (and lead to LTS) in the target cell. On the other hand, θ_{syn} must exceed V_{rest}, otherwise the sending cell would stay depolarized, and there could be no "release". P increases dramatically as θ_{syn} is decreased towards V_{rest}. Dashed curves correspond to the cases with τ_2 reduced or increased by a factor of 2. In the lower range for θ_{syn}, P varies proportionally with τ_2.

4 Discussion

We have presented a model of the LTS in thalamic neurons based upon the properties of the T-type Ca^{2+} current. Our model demonstrates that the T-type current along with a leakage current is sufficient to reproduce the characteristic features of the LTS. Our model neuron does not generate self-sustained oscillations under constant inhibition, unless the T-channel parameters are adjusted

away from their experimentally determined values (not demonstrated here). In fact, repetitive activity of thalamic relay neurons is perhaps not endogenous but rather is driven by phasic input from the nucleus reticularis. Therefore, we have been led to consider rhythmic oscillations in the nucleus reticularis, and whether these oscillations might be generated by synaptically coupled neurons [2]. We have formulated a two-cell model that exhibits oscillatory behavior, with a period (of about 100 ms) determined by the properties of the LTS and the inhibitory coupling between the two cells.

In our model system, the oscillation was found to be based on a "release" mechanism, that is, switching occurs when the depolarized cell falls below the presynaptic voltage threshold θ_{syn}, at the end of an LTS, so that a rebound excitation response is produced in its partner. In a separate study (in preparation), we show that a different mechanism, which may be called "escape", appears when certain parameters of the system are modified. In that case the slowly rising membrane potential of the inhibited cell reaches its threshold for rebound excitation and LTS generation before being "released" by the other cell. In contrast with the "release" case, when "escape" occurs, the switching in the alternating oscillatory pattern is determined by the dynamics of the inhibited cell. Hence, the parameter θ_{syn} does not modulate in a critical way the duration of inhibitory current, and the oscillatory period is insensitive to it. Either of these mechanisms should be considered candidates for the generation of rhythmic firing within regions of the central nervous system, like the nucleus reticularis, which have substantial inhibitory coupling between cells capable of rebound excitation.

Appendix

Our neuron model with two currents is described by a set of four ordinary differential equations:

$$C\dot{V} = -\bar{g}_{Ca}m^3h(V - V_{Ca}) - g_L(V - V_L) + I_{app} \quad (1)$$

$$\dot{m} = \alpha_m(1 - m) - \beta_m m \quad (2)$$

$$\dot{h} = \alpha_1(1 - d - h + Kh) \quad (3)$$

$$\dot{d} = \alpha_2(d - K(1 - d - h)) \quad (4)$$

where V is the membrane potential, m and h are the fractions in the open states O of the activation and inactivation gates, respectively, and d that of the deep closed state C_2 of the inactivation gate. $C = 1\mu\text{F/cm}^2$, $V_{Ca} = 120$ mV, $V_L = -65$ mV, and $g_L = 0.1$ mS/cm^2.

The voltage dependent functions are

$$\alpha_m(V) = \phi_m/[1.7 + \exp(-(V + V_s + 28.8)/13.5)], \quad (5)$$

$$\beta_m(V) = \alpha_m(V) \cdot \exp(-(V + V_s + 63)/7.8), \quad (6)$$

$$K(V) = (0.25 + \exp((V + V_s + 83.5)/6.3))^{1/2} - 0.5, \quad (7)$$

$$\alpha_1(V) = \phi_h \exp(-(V + V_s + 160.3)/17.8), \quad (8)$$

$$\alpha_2(V) = 1/[\tau_2(V)(1 + K(V))] \quad (9)$$

where $\tau_2(V) = (240/\phi_h)/[1+\exp((V+V_s+37.4)/30)]$. The temperature correction factors ϕ_m and ϕ_h, here for body temperature, have values 5 and 3, respectively. V_s depends on the extracellular Ca^{2+} concentration; here, $[Ca^{2+}]_o = 2.5$, $V_s = 2$ mV.

Other functions mentioned in the text can be expressed as follows: $m_\infty = \alpha_m/(\alpha_m + \beta_m)$, $\tau_m = 1/(\alpha_m + \beta_m)$, $h_\infty = 1/(1 + K + K^2)$, $\tau_1 = 1/\alpha_1(1 + K)$.

In Fig.1 $\bar{g}_{Ca} = 0.3$ mS/cm^2. For two-cell simulations (Figs.2-3), we use the simplification $m = m_\infty$; $\bar{g}_{Ca} = 1.1$ mS/cm^2, $\bar{g}_{syn} = 0.35$ mS/cm^2, $\theta_{syn} = -46$ mV, $k_{syn} = 2$ and $V_{syn} = -80$ mV.

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