Cellular Mechanisms Underlying Thalamic Augmenting Responses During 10 Hz Stimulation.

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Abstract

Repetitive stimulation of thalamic nuclei evokes augmenting responses in corresponding neocortical areas that increase in amplitude during the first few stimuli in a 7-14 Hz train (Dempsey and Morison, 1943). Possible mechanisms underlying the thalamic augmenting responses during repetitive stimulation were investigated with a computer model of a thalamic network including thalamocortical (TC) and thalamic reticular (RE) cells. The simplest network model demonstrating augmenting responses was a single pair of coupled RE and TC cells. Augmentation in this model was based on the progressive deinactivation of a low-threshold Ca^{2+} current in TC cells by RE-induced inhibitory postsynaptic potentials (IPSPs). The network properties of augmenting responses were analyzed in two reciprocally interacting chains of RE and TC cells. The augmentation shown in these models depended on $GABA_B$ IPSPs. Lateral $GABA_A$ inhibition between identical RE cells, which weakened bursts in these cells, diminished $GABA_B$ IPSPs and delayed the augmenting response in TC cells.

1 Introduction

Augmenting responses in the cortex have been elicited by rhythmic stimulation of white matter *in vivo* (Morin and Steriade, 1981) and in slices of rat motor cortex (Castro-Alamancos and Connors, 1996). Intracellular recordings have revealed an augmenting response generated in the thalamus after decortication (Steriade and Timofeev, 1997). *In vivo* recordings were performed in the ventro-lateral nucleus of dorsal thalamus as well as in rostro-lateral sector of reticular nucleus in adult decorticated cats anesthetized with ketamine and xylazine. Repetitive 10 Hz stimulation evoked the low-threshold augmenting responses in thalamic nuclei.

Our goal was to identify and analyze possible mechanisms underlying the thalamic augmentation with computer models. We explored, first, simple models that display the essential properties of augmentation and second, larger networks in which additional mechanisms arise.

2 Methods

2.1 Intrinsic currents

We examined single-compartment models of thalamocortical (TC) and thalamic reticular (RE) cells which included voltage- and calcium-dependent currents described by Hodgkin-Huxley kinetics:

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - I^{int} - I^{syn} \tag{1}$$

where $C_m = 1\mu/cm^2$ is the membrane capacitance, g_L is the leakage conductance ($g_L = 0.01mS/cm^2$ for TC cell and $g_L = 0.05mS/cm^2$ for RE cell), E_L is the reversal potential ($E_L = -70mV$ for TC cell and $E_L = -78mV$ for RE cell), I^{int} is a sum of active intrinsic currents (I_j^{int}) and I^{syn} is a sum of synaptic currents (I_j^{syn}). The area of RE cell was $S_{RE} = 1.43 \cdot 10^{-4}cm^2$ and the area of TC cell was $S_{TC} = 2.9 \cdot 10^{-4}cm^2$.

For both RE and TC cells we considered a fast sodium current I_{Na}, a fast potassium current I_K (Traub and Miles, 1991), a low-threshold Ca^{2+} dependent current I_T (Huguenard and Prince, 1992; Huguenard and McCormick, 1992), and a potassium leak current $I_{KL} = g_{KL}(V - E_{KL})$. A hyperpolarization-activated cation current I_h (McCormick and Pape, 1990; Destexhe et al., 1996) and potassium A current I_A (Huguenard et al., 1991) were also included in TC cells.

All intrinsic ionic currents $I_j^{int}(t)$ have the same general form:

$$I_j^{int} = g_j m^M h^N (V - E_j), \tag{2}$$

which depends on the maximal conductance g_j, the activation ($m(t)$) and inactivation ($h(t)$) variables, and the difference between membrane potential $V(t)$ and reversal potential E_j. The maximal conductances were $g_T = 1.75mS/cm^2$, $g_{Na} = 100mS/cm^2$, $g_K = 10mS/cm^2$ $g_{KL} = 0.005mS/cm^2$ for RE cell and $g_T = 2mS/cm^2$, $g_{Na} = 90mS/cm^2$, $g_K = 10mS/cm^2$ $g_{KL} = 0.012mS/cm^2$, $g_h = 0.02mS/cm^2$, $g_A = 1mS/cm^2$ for TC cell.

For both RE and TC cells the calcium dynamics is described by a simple first-order model (Destexhe et al.,1994a):

$$\frac{d[Ca]}{dt} = -AI_T - ([Ca] - [Ca]_\infty)/\tau, \tag{3}$$

where $[Ca]_\infty = 2.4 \cdot 10^{-4}mM$ is equilibrium calcium concentration, $A = 5.18 \cdot 10^{-5}mM \cdot cm^2/(ms \cdot \mu A)$ and $\tau = 5ms$.

2.2 Synaptic currents

$GABA_A$ and AMPA synaptic currents were modeled by first-order activation schemes (see review in (Destexhe et al., 1994b)). The current was given by

$$I_j^{syn} = g_j^{syn}[O](V - E_j^{syn}), \tag{4}$$

where g_j^{syn} is the maximal conductivity, E_j^{syn} is the reversal potential ($E_{AMPA}^{syn} = 0$ mV for AMPA receptors and $E_{GABA_A}^{syn} = -70$ mV for $GABA_A$ receptors). $[O](t)$ is the fraction of

open channels

$$\frac{d[O](t)}{dt} = \alpha(1 - [O](t))[T](t) - \beta[O](t), \tag{5}$$
$$[T](t) = A\theta(t_0 + t_{max} - t)\theta(t - t_0)$$

where $[T](t)$ is the concentration of the released transmitter, $\theta(x)$ is the Heaviside function, t_0 is a time instant of receptor activation, $A = 0.5$, $t_{max} = 0.3$ ms. The strength of $GABA_A$ synapses was $g_{GABA_A} = 0.02\mu S$. The maximal conductance of AMPA synapses was $g_{AMPA} = 0.1\mu S$.

$GABA_B$ receptors were described by a higher-order reaction scheme that took into account activation of K^+ channels by G-proteins (Destexhe et al., 1994b; Destexhe et al., 1996):

$$I_{GABA_B} = g_{GABA_B}\frac{[G]^4}{[G]^4 + K_d}(V - E_K), \tag{6}$$

$$\frac{d[R](t)}{dt} = K_1(1 - [R](t))[T](t) - K_2[R](t),$$

$$\frac{d[G](t)}{dt} = K_3[R](t) - K_4[G](t),$$

where $[R](t)$ is the fraction of activated receptors, $[G](t)$ is the concentration of G-proteins, $E_K = -95mV$ is potassium reverse potential. The maximal conductance of $GABA_B$ synapses was $g_{GABA_B} = 0.1\mu S$.

2.3 Network geometry

We considered a network consisting of two one-dimensional chains of RE and TC cells. Each TC cell was connected with its 9 nearest neighbors in the chain of RE cells and each RE cell was connected with 9 nearest neighbors from both chains of RE and TC cells (see Figure 1). All connections were identical and were described by eqs. (4)-(6). Reflective boundary conditions were used. Stimulation of thalamic cells was modeled by AMPA synapses which had a conductance $g_{ext} = 0.5\mu S$ for the center of stimulation and decayed exponentially with distance from the center with a ratio $k = 0.1$ between nearest neighbors on either side of the the center (see Figure 1). Some of the intrinsic parameters of the neurons in the network (g_{KL}, g_h for TC cells and g_{KL} for RE cells) were initialized with some random variability (variance $\sigma \sim 10\%$) to diminish the effect of lateral inhibition between reticular neurons and to insure the robustness of the results.

2.4 Computational methods

All simulations described in the paper were performed using fourth-order Runge-Kutta (RK(4)) method and in some cases embedded Runge-Kutta (RK6(5)) method (Enright et al., 1995) with time step 0.04 ms. Source C++ code was compiled on a Alpha Server 2100A (5/300) using GCC compiler (ver. 2.7.2.2). A simulation with 1 pair (2 cells) took 4 sec and a network with 27 pairs (54 cells) took 4.2 minutes of computer time to simulate 1 sec of real time.

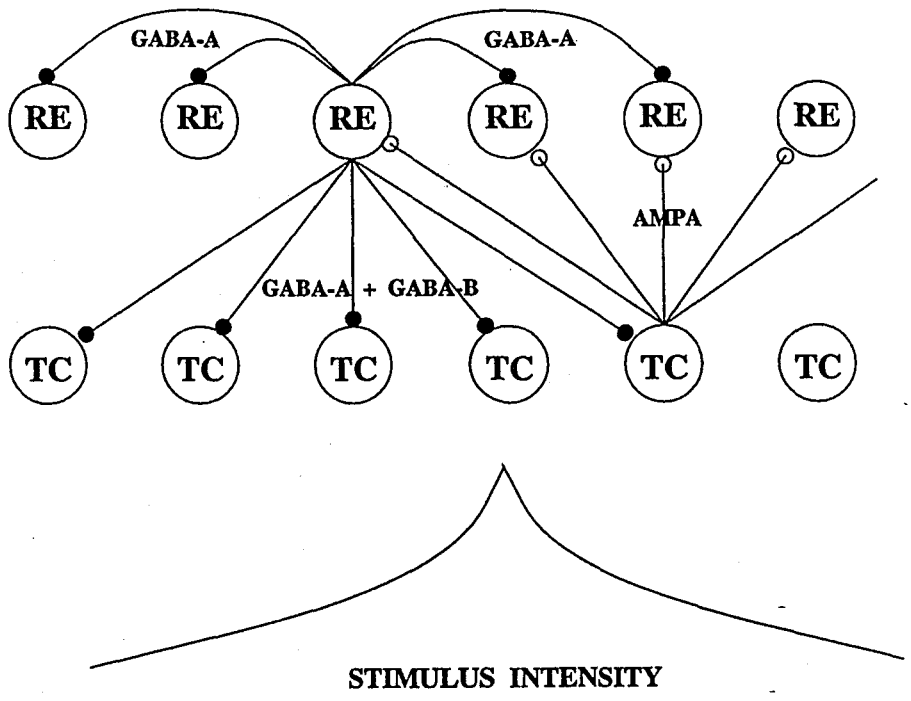

Figure 1: Two layers chain of RE and TC cells. The open circles mark the excitatory (AMPA) synapses and the filled circles mark the inhibitory ($GABA_A$ and $GABA_B$) synapses. The radius of connectivity for each of the projections was 9 cells.

3 Results

3.1 Augmenting responses in a reciprocal pair of RE-TC cells

The simplest network model demonstrating augmenting responses during repetitive stimulation was a pair of coupled RE and TC cells (see Fig. 2A). The external AMPA stimulus applied to TC cell produced an EPSP that evoked a sodium spike, which triggered a strong EPSP in the RE cell followed by a burst of spikes. The burst of spikes in the RE cell in turn produced $GABA_A$ and $GABA_B$ IPSPs in the TC cell. The IPSPs also partially deinactivated the low-threshold Ca^{2+} currents in the TC relay neuron. The next EPSP evoked by the external stimulus then produced a partial low-threshold calcium spike. Continuous stimulation progressively hyperpolarized the TC neuron due to summation of IPSPs, leading to enhancement of the low-threshold responses. The TC cell reached its maximal hyperpolarization at about the 4th-5th stimulus. The activation of I_h slightly repolarized the TC neuron, which could decrease the level of activation of low-threshold responses.

Figure 2B shows the response of two coupled pairs of RE-TC cells on the repetitive TC cells stimulation. All cells were identical and both TC cells were stimulated equally. Lateral $GABA_A$ inhibition between identical RE cells weakened the bursts in these cells, which diminished the $GABA_B$ IPSPs and delayed the augmenting response in TC cells (compare Fig.2A and Fig.2B).

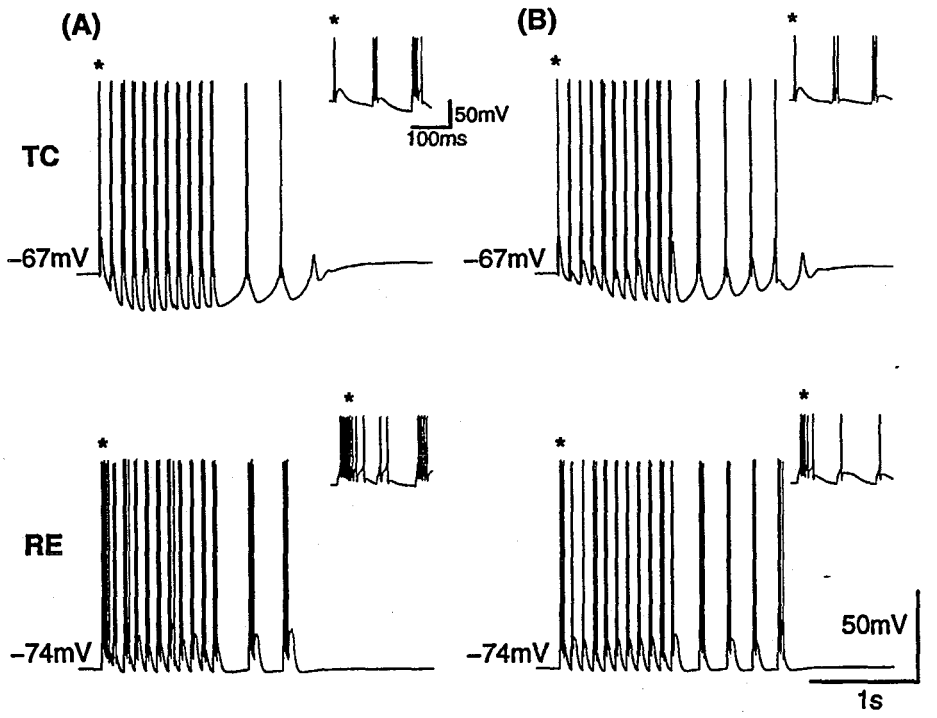

Figure 2: Computer simulation of the low-threshold augmenting responses in a simple thalamic circuits. (A) One RE-TC pair. (B) Two coupled pairs of identical RE-TC cells. In this case the augmenting response was delayed because of the lateral inhibition between RE cells.

3.2 Augmenting responses in chains of RE-TC cells

Two chains of 27 RE and 27 TC cells were analyzed to characterize properties of augmenting responses in this network. For repetitive 10 Hz stimulation the pool of thalamic cells showed incremental increases in activity during the first 3-4 stimuli in the train of 11 shocks (Figure 3). This was manifest in the progressively increasing number of spikes per burst in the TC cells and by the recruitment of more TC cells firing action potentials. TC cells remote from the stimulation site also participated in the augmenting response after a delay through TC-RE-TC interactions. When both RE and TC cells were stimulated by the train, the additional stimulation of RE cells increased the low-threshold augmenting response by reinforcing $GABA_B$ IPSPs in TC cells.

The simulated train of 11 shocks was followed by a sequence of slow (3-4Hz) oscillations elicited by interactions between RE and TC cells. Reducing the $GABA_B$ IPSPs in TC cells (by decreasing the conductance of $GABA_B$ synapses and increasing the conductance of lateral $GABA_A$ synapses) delayed the augmenting responses in TC cells and decreased the depth of hyperpolarization in TC cells during stimulation. As a result, the frequency of post-stimulus oscillations in TC cells was increased to 7-14 Hz (not shown).

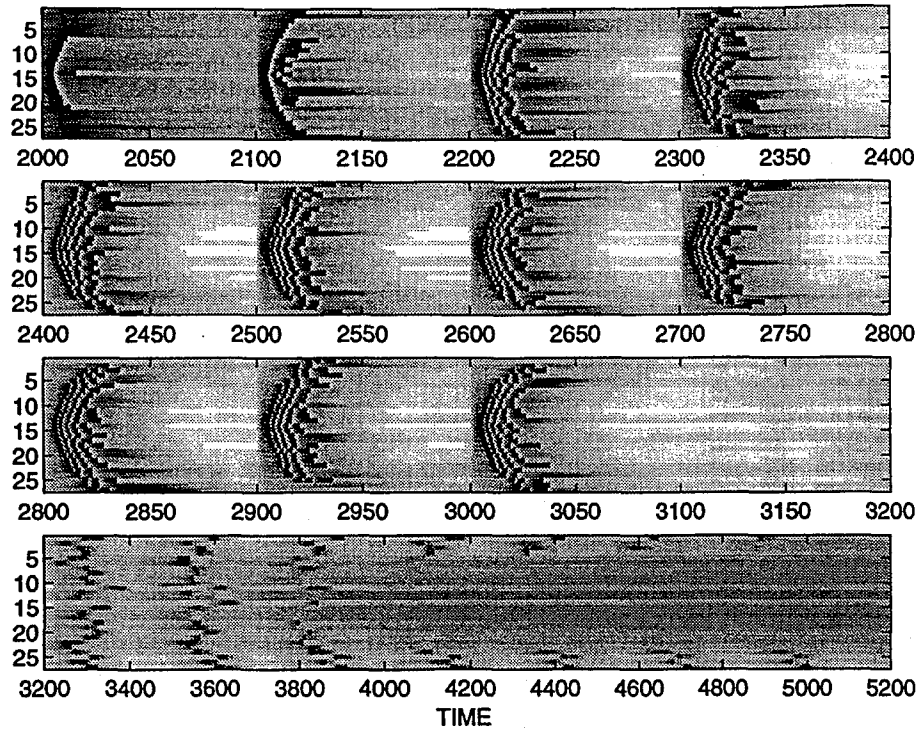

Figure 3: The responses of 27 TC cells during 10 Hz stimulation in chains of interacting RE and TC cells. The first three shocks in the train of 11 shocks evoked incremental responses in TC cells. The lowest panel shows a slow 3-4 Hz post-stimulus oscillations. The value of the membrane potential for each neuron was coded by using a white-black scale ranging from -90mV (white) to -30mV (black).

4 Discussion

In vivo recordings from the dorsal thalamus of decorticated cats anesthetized with ketamine and xylazine have revealed a low-threshold augmenting response generated in the thalamus after decortication (Steriade and Timofeev, 1997). Augmentation was characterized by a progressive hyperpolarization of TC cells during repetitive stimulation. The model of the thalamic network examined in this paper shows that both synaptic interactions and intrinsic currents in contribute to generating augmenting responses. A thalamic stimulus produces an EPSP followed by the RE-induced IPSP in the TC cell which deinactivates the low-threshold Ca^{2+} current. The next EPSP then is followed by the low-threshold spike. Progressive recruitment of TC cells the network occurs through $GABA_B$ IPSP responses.

The strength of the $GABA_B$ IPSP is an important parameter for controlling the development of augmenting responses. Reducing the RE-evoked $GABA_B$ IPSP reduced the partial deinactivation of the low-threshold Ca^{2+} current and delayed the augmenting responses in TC cell. Simultaneous stimulation of thalamic and reticular nuclei increased the duration of the burst discharges in RE cells which led to the strengthening of $GABA_B$ IPSPs and more rapid augmentation of responses in TC cells.

In contrast to thalamic stimulation, repetitive stimulation of prethalamic nuclei evokes weak augmenting responses in thalamic relay cells (not shown). Based on the computer

model, we propose that one of the reasons for such a difference is that in the experiments with prethalamic shocks there might have been exclusive monosynaptic stimulation of the thalamic relay cells. This could be tested by recording from RE cells in this nucleus.

In *in vivo* experiments, thalamic stimulation with thalamic shocks evokes synchronous activation of thousands of RE cells and results in strong $GABA_B$ IPSPs in related TC cells. In the absence of strong stimulation, the spatio-temporal coherence in the thalamocortical network is much too low to produce strong activation of the $GABA_B$ receptors and as a consequence the $GABA_B$ IPSPs should be reduced in TC cells.

In a cortical slice preparation, it has been shown that the activation of $GABA_B$ IPSPs can be achieved only by bursts of presynaptic spikes from inhibitory interneurons (Thomson et al., 1996). During naturally occurring spindles the interaction between thalamic and reticular nuclei is determined mainly by $GABA_A$ and AMPA currents. In the present model the size of thalamic pool is highly limited and the effects of strong $GABA_B$ inhibition were taken into account by increasing the maximal conductance for $GABA_B$ synapses. This gives a fast augmentation of the responses in TC cells during a train of stimuli; however, the spindle oscillations evoked by a single thalamic shock is transformed after a few cycles into slow (3-4Hz) oscillations.

The results of the simulations reported here indicate that the basic electrophysiological properties of thalamic cells and intrathalamic circuitry can produce significant intrathalamic short-term plasticity.

Acknowledgments

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