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Reciprocal inhibition controls the oscillatory state in thalamic networks

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Abstract

The thalamus plays a central role in the genesis of both normal spindle oscillations and pathological absence seizures. Inhibitory connections between neurons of the thalamic reticular (RE) nucleus help to prevent seizures. Much modeling and experimental work has focused on the proposal that intra-RE inhibition shortens RE cell bursts, and that when prolonged bursts occur, they activate $GABA_B$ receptors, transforming spindle oscillations into absence seizures. Here, we present an alternative model in which intra-RE inhibition prevents epileptiform thalamic activity by desynchronizing RE cell bursts, rather than by controlling their duration.

Keywords: Absence epilepsy; Spindle rhythm; Synchrony; Thalamus

1. Introduction

The thalamus plays a central role in the genesis of both normal spindle oscillations and pathological absence seizures. Interactions between excitatory thalamocortical (TC) neurons and inhibitory neurons of the thalamic reticular (RE) nucleus generate spindles [16] and may contribute to absence seizures [12]. By contrast, inhibitory connections between neurons of the thalamic RE nucleus are thought to prevent seizures. The anti-absence drug clonazepam (CZP) suppresses evoked oscillatory activity in thalamic slices by enhancing intra-RE inhibition [11]. In knockout mice lacking the $\beta 3$ subunit of the $GABA_A$ receptor, inhibitory synapses between RE cells are selectively disrupted, while those from RE cells to TC cells are normal [13]. As a result, oscillations in thalamic slices from $\beta 3^{-/-}$ mice last longer and are more synchronized than those from

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wild-type slices. Consistent with the hypothesis that such vigorous thalamic activity contributes to absence seizures, $\beta 3^{-/-}$ mice have spontaneous absence-like seizures [5].

Several researchers have focused on prolonged bursting by RE cells and $GABA_B$ receptor activation in TC cells as the key elements which transform spindle oscillations into spike-wave seizures. This hypothesis is based on experiments using the $GABA_A$ receptor antagonist bicuculline in ferret thalamic slices. After bicuculline application, RE cells fire prolonged bursts, and spindle oscillations are transformed into synchronized, slow $GABA_B$ receptor-mediated oscillations that resemble spike-wave discharges [16]. This has led to the hypothesis, supported by modeling, that intra-RE inhibition shortens RE cell bursts, and that when these bursts become prolonged, $GABA_B$ receptors are activated in TC cells, resulting in epileptiform discharges in vitro or absence seizures in vivo [6,7–9,14].

However, two recent findings have called this mechanism into question. First, in addition to blocking $GABA_A$ receptors, bicuculline also blocks the Ca^{2+}-dependent K^+ current, $I_{K(Ca)}$ [4]. Blocking $I_{K(Ca)}$ is sufficient to prolong RE cell bursts, so it is not clear to what extent the block of intra-RE inhibition alone prolongs RE cell bursts. Second, during seizures in a rat model of absence epilepsy, local application of the $GABA_B$ receptor antagonist CGP55845A has no effect on TC cell firing [15]. Thus, the mechanism by which intra-RE inhibition prevents seizures remains unclear.

Here we present a thalamic network model in which intra-RE inhibition controls the pattern, rather than the duration, of RE cell bursts. When intra-RE inhibition is present, RE cells burst irregularly and out-of-phase, producing spindle-like oscillations in the network. In contrast, when intra-RE inhibition is absent, RE cells burst regularly and synchronously, producing epileptiform activity that does not depend on $GABA_B$ receptors.

2. Methods

The model is based on that of Sohal et al. [14]. Briefly, we studied a network which included 100 RE and 100 TC cells, each of which was modeled as a single compartment. Each TC cell contained a leak current, a low-threshold Ca^{2+} current (I_T), Na^+ and K^+ currents underlying action potentials, a hyperpolarization-activated cationic current (I_h), and a $GABA_A$ receptor-mediated current. Each RE cell contained a leak current, a low-threshold Ca^{2+} current (I_{Ts}), Na^+ and K^+ currents underlying action potentials, a Ca^{2+}-dependent K^+ current ($I_{K(Ca)}$), a $GABA_A$ receptor-mediated current, and an AMPA receptor-mediated current. Except for $I_{K(Ca)}$, detailed kinetics for all currents are presented in Sohal et al. [14]. The conductance of $I_{K(Ca)}$ was proportional to the intracellular $[Ca^{2+}]$, which decayed via first-order kinetics, with a time constant of 100 ms. These kinetics reproduce the burst AHP observed in several studies of RE cells [1–3]. RE and TC cells were organized into two linear arrays, and all connections were local and topographic, e.g. each RE cell inhibited the eight nearest RE cells and the four nearest TC cells, etc. All simulations were run using NEURON [10] at a temperature of 34°C and with a time step of 0.1 ms.

3. Results

The model reproduces spindle-like oscillations by a well-established cycle of events: RE cells burst, inhibiting TC cells, which then rebound burst, exciting RE cells, so that they burst again. Fig. 1 (left) shows the activity of RE cells (top) and TC cells (bottom) during spindle-like oscillations. Note that while individual cells burst repetitively, inter-burst intervals are somewhat irregular, and the times of bursts are desychronized across the network.

In contrast to these spindle-like oscillations, epileptiform activity emerges in the absence of intra-RE inhibition. Fig. 1 (right) shows the activity of RE cells (top) and TC cells (bottom) in the same network, after the $GABA_A$ receptor conductance on RE cells has been set to zero, eliminating intra-RE inhibition. In this case, cells burst repetitively, the inter-burst intervals are very regular, and the times of bursts are synchronized across the network. Note that both the network with and the one without intra-RE inhibition started from the same initial condition, in which a subset of RE cells were depolarized to elicit bursts.

Fig. 2 plots the total number of TC cell spikes (within a 10 ms window) as a function of time for the network with (solid line) and without (dotted line) intra-RE inhibition. In the network with intra-RE inhibition, TC cell activity rises and falls irregularly,

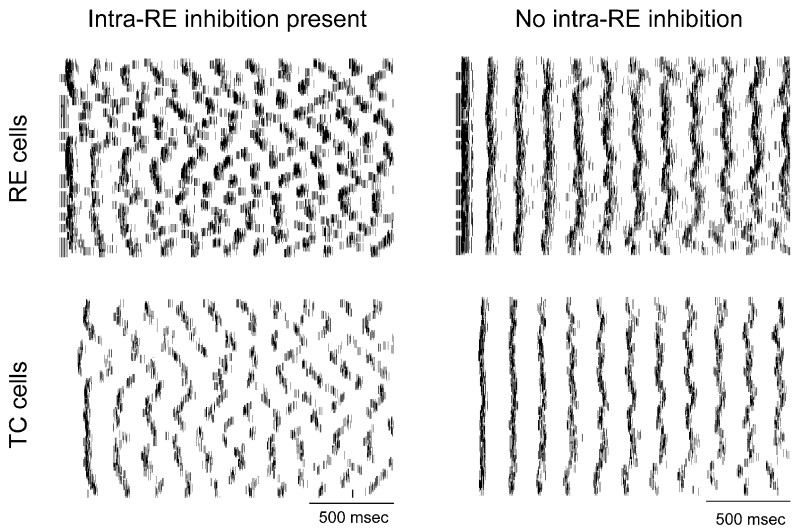

Fig. 1. Simulated activity in thalamic networks with (left) and without (right) intra-RE inhibition. In each case, the top and bottom panels shows activity of model RE cells and model TC cells, respectively. Each mark indicates the time at which an individual cell fires an action potential. Time runs horizontally and location in the network runs vertically, so that a horizontal row represents the spike train of a single cell. Both networks are initialized with the same starting conditions. However, activity in the network with intra-RE inhibition (left) rapidly settles into a desynchronized, spindle-like mode, in which the timing of bursts in an individual RE or TC cell is irregular. In contrast, in the network without intra-RE inhibition (right), activity remains highly synchronized in a seizure-like mode, such that bursts occur nearly simultaneously across the network.

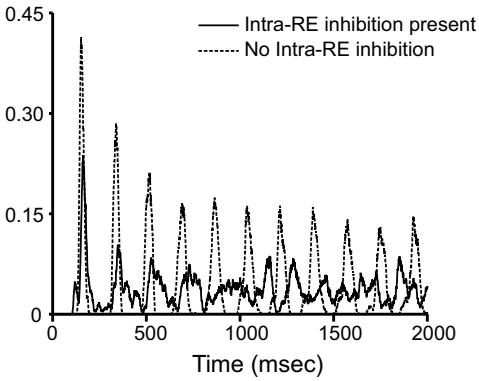

Fig. 2. The total number of TC cell spikes (within a 10 ms window) as a function of time for the network with (solid line) and without (dotted line) intra-RE inhibition (the number of spikes is normalized by the number of cells in the network). As in Fig. 1, both networks start from the same initial condition. The network with intra-RE inhibition rapidly settles into a desynchronized state in which TC cell activity rises and falls irregularly. By contrast, the network without intra-RE inhibition remains synchronized, so that there are sharp, high-amplitude peaks of TC cell activity, the intervals between peaks are relatively constant, and spike-free periods occur between peaks.

whereas in the network without intra-RE inhibition, there are sharp, high-amplitude peaks of TC cell activity, the intervals between peaks are relatively constant, and spike-free periods occur between peaks. Thus, the spindle- and seizure-like modes of activity can be clearly differentiated on the basis of summed activity of TC cells throughout the network.

In Fig. 3, membrane potentials of several representative cells are shown in order to illustrate how intra-RE inhibition prevents the emergence of epileptiform activity. On the left are membrane potentials of cells in the network with intra-RE inhibition. The top panel shows membrane potentials from two RE cells at opposite ends of the network, while the bottom panel shows membrane potentials from corresponding TC cells. Note that the two RE cells burst repetitively, but that the bursts occur irregularly and are desynchronized in the two RE cells. In particular, some EPSPs fail to elicit bursts in these RE cells (arrows in Fig. 3). Intra-RE inhibition causes these failures. Sometimes when an EPSP arrives in an RE cell, that RE cell is receiving inhibition from other RE cells that have already begun to burst. This inhibition shunts the EPSP so that it fails to evoke a burst. In this way, intra-RE inhibition reduces the number of RE cells that burst in-phase with each other.

After an RE cell bursts, its T-current becomes inactivated. Hence, when an RE cell fails to burst in response to excitatory input, its T-current is deinactivated to a relatively large extent. As a result, that RE cell tends to burst rapidly the next time that excitatory input arrives. This RE cell will then inhibit other RE cells, possibly preventing them from bursting. Thus, RE cells that fail to burst in response to an excitatory input tend to burst in response to subsequent excitation. Conversely, when an RE cell does burst

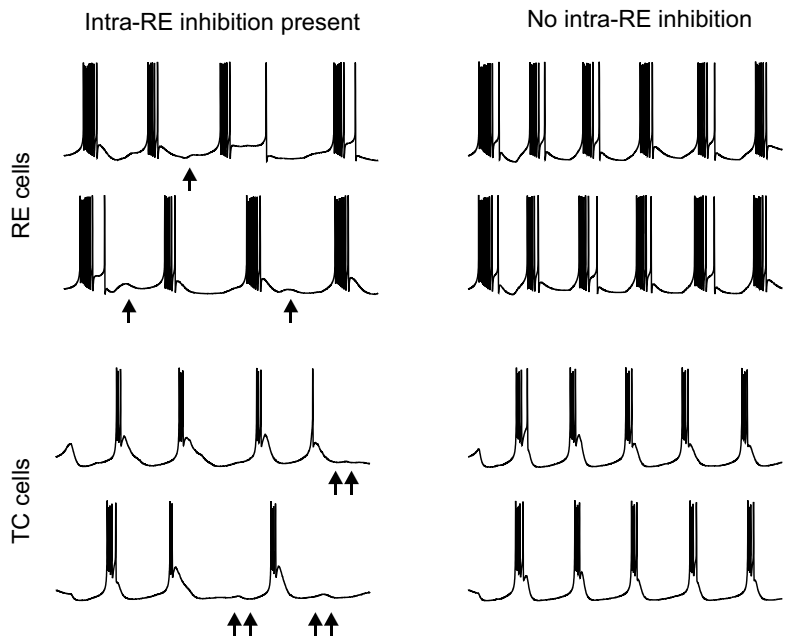

Fig. 3. Membrane potentials of model RE (top) and TC (bottom) cells during simulated activity in thalamic networks with (left) and without (right) intra-RE inhibition. For each case, the membrane potentials of two RE or TC cells, from opposite ends of the same network, are shown. Note that in the network without intra-RE inhibition (right), RE cells burst regularly and synchronously, producing robust IPSPs in TC cells which consistently rebound burst. In contrast, when intra-RE inhibition is present (left), RE cells occasionally fail to burst in response to excitatory input (indicated by arrows). As a result, RE cells burst at irregular intervals, and bursts are desynchronized in the two depicted RE cells. Because RE cell bursting is poorly synchronized, TC cells receive weak IPSPs and rebound burst irregularly. In particular, because RE cells burst out-of-phase, sometimes a second IPSP arrives before a TC cell has rebound burst in response to a previous IPSP. This leads to cycles on which the TC cell fails to rebound burst (indicated by double arrows). Irregular TC cell bursting produces weak excitatory input to RE cells, further desynchronizing network activity.

in response to excitatory input, it is less likely to burst subsequently. This makes RE cell bursting irregular.

Desynchronized and irregular RE cell bursts affect the pattern of TC cell bursting. When RE cell bursts are not synchronized and sometimes fail to occur, TC cells receive weak IPSPs that occasionally fail to elicit rebound bursts. In particular, because RE cell bursting is desynchronized, IPSPs can arrive in a TC cell out-of-phase. Thus, sometimes when a TC cell is about to rebound burst in response to one IPSP, a second IPSP arrives, preventing the rebound burst (double arrows in Fig. 3). This irregular TC cell bursting results in weak excitatory feedback to RE cells, exacerbating irregular RE cell bursting. Thus, intra-RE inhibition, by shunting excitatory input to RE cells, shifts the network into a desynchronized, spindle-like oscillatory mode.

Contrast the membrane potentials of cells in this spindle-like mode with those in the network without intra-RE inhibition (Fig. 3, right). Again, the top panel depicts membrane potentials from two RE cells at opposite ends of the network while the bottom panel shows the membrane potentials of corresponding TC cells. In this network, the two RE cells burst synchronously and regularly. As a result, TC cells receive robust inhibition that consistently elicits synchronous rebound bursts. Thus, in the absence of intra-RE inhibition, the network produces regular, synchronized epileptiform discharges.

Note that while intra-RE inhibition controls the pattern of RE cell bursting, it does not affect the duration of individual RE cell bursts. In this model, accumulation of calcium during a burst activates $I_{K(CA)}$ in RE cells, which terminates the burst and produces the burst afterhyperpolarization seen in Fig. 3. Thus, intra-RE inhibition does not play a major role in burst termination.

Preliminary recordings from RE cells during evoked oscillations in rat thalamic slices support this idea (Sohal and Huguenard, unpublished observations). During control oscillations, RE cells fail to burst on many cycles. However, following the application of the selective $GABA_A$ receptor antagonist picrotoxin (PTX), which does not affect $I_{K(Ca)}$ [4], RE cells burst more often. Although RE cell bursts occur more frequently in PTX, the number of spikes in each of these bursts remains unchanged. Similarly, in most cases, PTX has little or no effect on the number of spikes fired by RE cells in response to internal capsule stimulation.

4. Conclusions

We have developed a thalamic network model in which intra-RE inhibition controls the pattern, rather than the duration, of RE cell bursts. As a result, the network oscillates in different modes depending on the level of intra-RE inhibition. When intra-RE inhibition is present, RE cells burst irregularly, generating desynchronized, spindle-like activity. In contrast, when intra-RE inhibition is absent, RE cells burst regularly and synchronously, producing epileptiform discharges.

This differs from earlier models in two ways. First, previous models did not include $I_{K(CA)}$ in RE cells, and, as a result, when intra-RE inhibition was weak or absent, RE cells fired prolonged bursts [6–9]. By contrast, $I_{K(CA)}$ limits the duration of RE cell bursts in this model, so that these bursts do not become prolonged in the absence of intra-RE inhibition. Second, in previous models, activation of $GABA_B$ receptors on TC cells was the key element underlying epileptiform activity in the thalamus [6–9], whereas this model simulates epileptiform activity without including $GABA_B$ receptors. Thus, this model provides a novel mechanism in which intra-RE inhibition prevents absence seizure genesis by desynchronizing thalamic activity.

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