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# Reciprocal inhibitory connections produce desynchronizing phase lags during intrathalamic oscillations☆

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**Abstract**

In $GABA_A$ $\beta_3$ knockout mice ($\beta_3^{-/-}$), inhibitory synapses between thalamic reticular (RE) neurons are selectively impaired. Consequently, oscillations in thalamic slices from $\beta_3^{-/-}$ mice last longer and are more synchronized than those from wild-type mice (Huntsman et al., Science 283 (1999) 541). We used computational models to study mechanisms by which intra-RE inhibition abbreviates and desynchronizes intrathalamic oscillations. Intra-RE inhibition could produce the former effect by shunting recurrent excitation. Intra-RE inhibition could produce the latter effect by changing the duration, but not the timing, of RE cells' bursts. These results suggest mechanisms by which intra-RE inhibition prevents hypersynchrony characteristic of absence epilepsy. 

*Keywords:* Thalamus; Spindle rhythm; Absence seizures; Angelman syndrome; $GABA_A$ receptors

## 1. Introduction

The thalamus participates in a wide range of thalamocortical oscillations including 7–14 Hz sleep spindles [1,2,8,10,11]. Several experimental observations suggest that reciprocal inhibitory connections between thalamic reticular (RE) neurons regulate thalamic spindle oscillations and prevent hypersynchrony characteristic of some

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epilepsies. The anti-absence drug, clonazepam, may function by enhancing $GABA_A$ connections between RE cells [5,6]. Additional evidence comes from mice lacking the $\beta_3$ subunit of the $GABA_A$ receptor. Knockout of the $\beta_3$ subunit reduces the strength and duration of $GABA_A$ synapses between RE cells without affecting those from RE to TC cells [7]. This highly selective change has important consequences for intrathalamic oscillations elicited by stimulation of internal capsule in vitro [7]. First, oscillations last much longer in thalamic slices from knockout ($\beta_3^{-/-}$) mice than in those from wild-type ($\beta_3^{+/+}$) animals. Second, phase differences between TC cell activity at different locations along knockout slices are negligible. In wild-type slices by contrast, the activity of TC cells becomes progressively phase lagged with increasing distance from the center. The phase lags observed in wild-type slices are at least an order of magnitude larger than those in knockout slices. The exact mechanisms by which intra-RE inhibition shortens and desynchronizes intrathalamic oscillations are not clear. Here we use computational models to study mechanisms for these two effects.

## 2. Methods

We studied a network model with 400 thalamocortical (TC) and 400 thalamic reticular (RE) neurons. Models for both types of neurons were presented in an earlier study [9]. The network had a one-dimensional architecture with neurons distributed evenly along a straight line in two layers (one layer consisted of RE cells, the other of TC cells). The network models a slice 1 mm in length, i.e. the distance between adjacent model cells corresponds to 5 μm along a thalamic slice. We used reflexive boundary conditions, so a neuron at position zero is at the center, not the edge, of the model slice. The network included three sets of connections: $GABA_A$ synapses from RE to TC cells, $GABA_A$ synapses between RE cells, and AMPA synapses from TC to RE cells. All connections were local and topographic. The kinetics of $GABA_A$ currents were based on intracellular recordings [7]. All simulations were run using NEURON [4] at a temperature of 32°C and with a time step of 0.1 ms.

## 3. Results

### 3.1. Intra-RE inhibition shortens and desynchronizes intrathalamic oscillations

Fig. 1 depicts activity in wild-type and knockout networks, respectively. In both networks activity is elicited by exciting a random subset of RE cells above threshold. The probability of activation is highest for RE cells at position zero (which represents the center of the model slice), and decreases with increasing distance from the center of the model slice. Following activation of RE cells, the model reproduces two experimentally observed differences between responses in wild-type slices and those in knockout slices [7]. First, in the knockout network, interactions between RE and TC cells sustained an intrathalamic oscillation for the duration of the simulation (600 ms), whereas activity in the wild-type network had a much shorter duration.

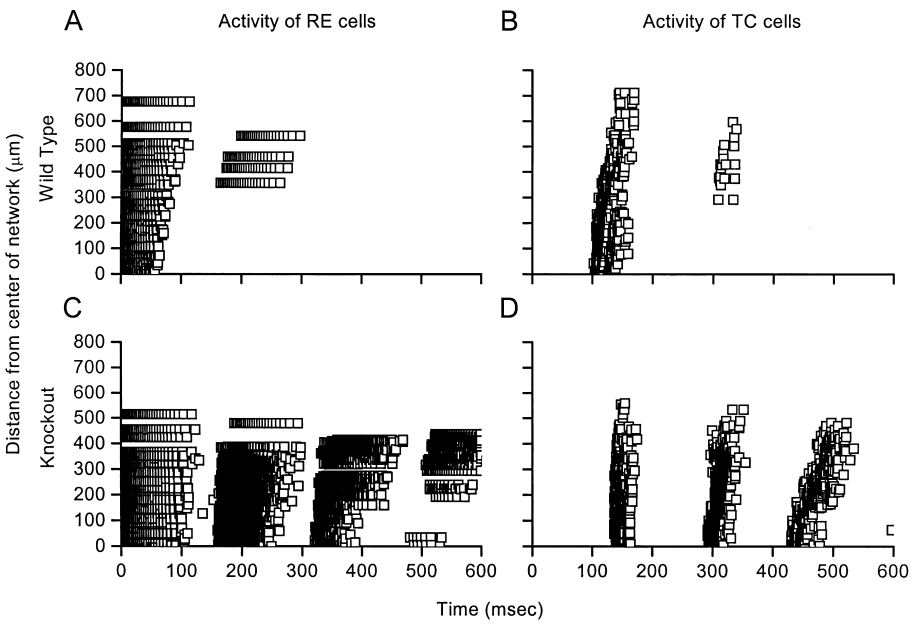


Fig. 1. Intrathalamic oscillations are shorter and less synchronized in a wild-type network than in a knockout network. (A) The times at which RE cells in a wild-type network spike are plotted as a function of distance from the center of the model slice. RE cells' bursts are longer lasting towards the periphery than near the center. (B) The times at which TC cells spike in a wild-type network are plotted as a function of distance from the center of the model slice. The spatial gradient in the duration of RE cells' bursts produces a corresponding gradient in the timing of TC cell bursts. (C) The times at which RE cells spike in a knockout network. In this network the durations of RE cells' bursts are relatively uniform across the network, especially during the first two cycles. (D) The times at which TC cells spike in a knockout network. Because the durations of RE cells' bursts are relatively uniform in this network, TC cells' bursts are nearly simultaneous on the first two cycles.

A second difference is that whereas TC cell activity in knockout networks is highly synchronized, in wild-type networks, TC cell activity becomes progressively phase lagged with increasing distance from the center of the model slice. To make the latter observation precise, we found the phase lag of TC cell activity at various points along the model slice relative to activity at the center of the model slice using cross-correllograms. These phase lags are plotted as a function of distance in Fig. 2. In wild-type networks, phase lags increase with distance, reaching 29 ms at 500 μm, whereas phase lags in knockout networks remain under 8 ms over the same distances.

Fig. 1A shows that in the wild-type network, RE cells' bursts are much shorter near the center of the model slice than towards the periphery. In contrast, Fig. 1C shows that RE cells' bursts are of approximately uniform duration throughout the knockout network. These observations can be explained as follows. Near the center of the model slice, the initial stimulus activates many RE cells. In the wild-type network, this produces a central level of intra-RE inhibition that is eventually strong enough to shunt RE cells' T-current and hasten the end of their bursts. This is shown by Fig. 3,

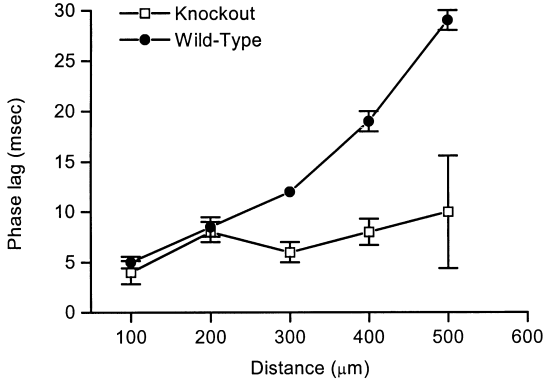


Fig. 2. TC cell activity becomes progressively phase lagged (relative to TC cell activity at the center of the slice) with increasing distance from the center of the model slice. These distance-dependent phase lags are much larger in wild-type networks than in knockout networks.

which plots the synaptic currents and membrane potentials of two RE cells, one near the center of the model slice and one towards the periphery. The central RE cell's burst ends early (Fig. 3B), when IPSC conductance is relatively large (Fig. 3A, solid line). Towards the periphery of wild-type slices, few RE cells are active, so intra-RE inhibition is weak (Fig. 3A, dashed line). As a result, the peripheral RE cell's burst outlasts the central RE cell's burst (Fig. 3C). In knockout networks, by contrast, intra-RE inhibition is nowhere strong enough to shunt RE cells' bursts.

These different RE cell burst durations explain the differences between phase lags in wild-type and knockout slices. In wild-type networks, the progressive lengthening of RE cells' bursts with increasing distance from the center of the model slice produces a corresponding phase gradient in the time of TC cells' rebound bursts. In contrast, the duration of RE cells' bursts is relatively uniform across a knockout network, and hence TC cell activity is synchronous across large distances.

Fig. 3 also helps to explain why activity has a much shorter duration in wild-type networks than in knockout networks. Rebound bursts in TC cells elicit EPSPs in the centrally located RE cell, whose membrane potential is plotted in Fig. 3B. However, comparing the synaptic currents with the membrane potential reveals that when the EPSPs arrive (arrow in Fig. 3B), many $GABA_A$ channels are still open (arrow in Fig. 3A). As a result the EPSPs are shunted. Fig. 3D shows how this shunting affects another centrally located RE cell (one which is not activated on the first cycle). In the knockout network, the return EPSPs are sufficient to elicit a burst in this RE cell. However, in the wild-type network, the same RE cell fails to burst, because the EPSPs have been shunted.

### *3.2. Intra-RE inhibition can prevent, but not delay, RE cell bursts*

The preceding results elucidate one mechanism by which intra-RE inhibition could produce phase gradients in thalamic networks. We refer to this mechanism, in which

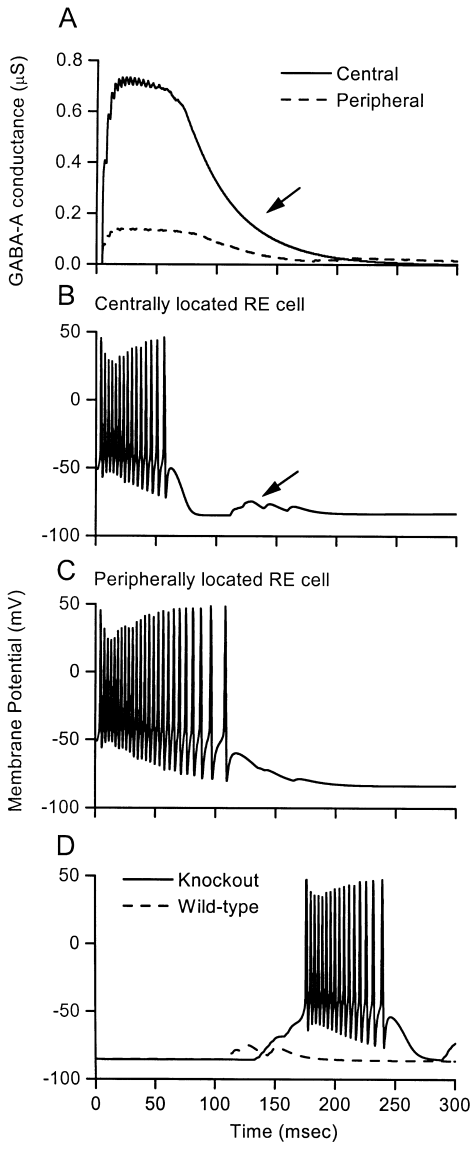


Fig. 3. In wild-type networks, intra-RE inhibition shortens the duration of bursts in centrally located RE cells and shunts subsequent excitatory input to RE cells. (A) Time courses of the total inhibitory synaptic currents plotted for RE cells at the center (solid line) and periphery (dashed line) of the model slice. (B) Intra-RE inhibition shortens the burst in this centrally located RE cell, and shunts subsequent EPSPs (indicated by arrow) in this cell. (C) In the periphery, the level of intra-RE inhibition is low, so this RE cell bursts for an extended duration. (D) Membrane potential of an RE cell in a knockout network (solid line) and the same RE cell in a wild-type network (dashed line). In the wild-type network, intra-RE inhibition shunts EPSPs, preventing the RE cell from bursting.

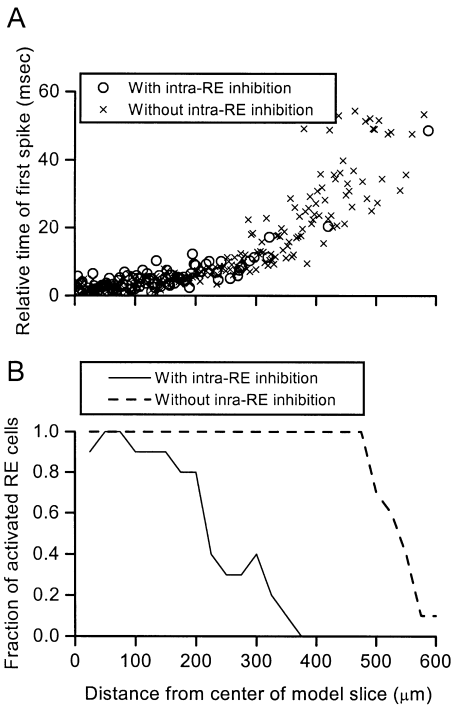


Fig. 4. Intra-RE inhibition during the initiation of RE cells' bursts can affect which RE cells burst, but not the time at which bursts begin. (A) The relative times at which RE cells begin to burst are plotted for networks with (open circles) and without (crosses) intra-RE inhibition. (B) The fraction of RE cells bursting is plotted as a function of distance. In the network with intra-RE inhibition (solid line), the boundary between RE cells which do burst and those which do not is much closer to the center of the model slice than in the network without any intra-RE inhibition (dashed line).

$GABA_A$ currents hasten the end of central RE cells' bursts, as "late shunting". However, additional mechanisms might also contribute to intrathalamic phase differences. For example, if the strength of excitatory input to RE cells decreases with increasing distance from the center of the model slice, then centrally located RE cells will burst before their more peripherally located counterparts. Intra-RE inhibition could amplify such shunting-independent phase delays. Earlier-bursting, central RE cells might inhibit later bursting, peripheral RE cells, further delaying the beginning of bursts in those peripheral RE cells. We refer to this as "early shunting".

To test whether early shunting occurs, we compared the times at which RE cells start bursting in a normal network to those in the knockout network. These times are plotted in Fig. 4 (RE cells in both networks receive the same spatially graded input). As Fig. 4 shows many more peripherally located RE cells burst in the knockout network than in the normal network. However, RE cells that do burst in both networks begin to do so at essentially the same time. Thus, intra-RE inhibition can affect the population of RE cells that burst, but not the times at which bursting cells begin to burst.

## 4. Discussion

Using a computational model that incorporates intracellular data about the strength and kinetics of synaptic currents in thalamic slices from wild-type ($\beta_3^{+/+}$) and knockout ($\beta_3^{-/-}$) mice [7], we studied a mechanism by which intra-RE inhibition shortens the duration of intrathalamic activity, and two mechanisms by which intra-RE inhibition might desynchronize such activity. We observed that:

1. Intra-RE inhibition produces a spatial gradient in the durations of RE cells' bursts through late shunting.
2. Early shunting of input to RE cells by intra-RE inhibition does not significantly affect the time at which RE cells begin to burst.
3. Inhibitory currents can shunt return EPSPs in RE cells, preventing sustained intrathalamic oscillations.

### *4.1. Implications for thalamocortical oscillations*

These results suggest mechanisms by which intra-RE inhibition might prevent hypersynchronous activity characteristic of some epilepsies. Earlier modeling studies have suggested a critical role for prolonged RE cell bursts during spike and wave seizures [3]. We have shown that intra-RE inhibition could reduce RE cell discharge by shortening RE cells' bursts (e.g. Fig. 2) and/or shunting subsequent excitatory input to RE cells, preventing them from bursting (e.g. Fig. 3). Phase gradients in TC cell activity due to intra-RE inhibition might also prevent temporal summation of TC cell input to cortical pyramidal cells.

### *4.2. Predictions*

We predict that stimulation of internal capsule should activate many RE cells in one particular region of the thalamic slice (hereafter referred to as the "center" of the slice) and activate fewer RE cells with increasing distance from the center. Because of resulting differences in the amount of intra-RE inhibition, in the central region, RE cells' bursts should be shorter than at the periphery. In contrast, RE cells' bursts should be relatively long across knockout slices.

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