SYNCHRONIZING AND DESYNCHRONIZING EFFECTS OF INHIBITION DURING THALAMIC OSCILLATIONS

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Oscillations are ubiquitous in neural systems, and synchronized activity during network oscillations may play a role in cognitive processes (Fries et al., 2001; Ohara et al., 2001; Rodriguez et al., 1999; Tallon-Baudry et al., 2001), and epilepsy (Huntsman et al., 1999; Steriade et al., 1993). In many cases, inhibitory networks regulate the spatiotemporal properties of neural oscillations. A fundamental issue is under what conditions inhibition synchronizes or desynchronizes oscillatory activity.

Inhibition plays an essential role during spindle oscillations in thalamic slices which occur via the following mechanism: burst firing in GABAergic neurons of the thalamic reticular nucleus (TRN) produces IPSPs in thalamocortical (TC) neurons located in thalamic relay nuclei. These neurons contain a low-threshold, T-type Ca^{2+} current that is deinactivated by sufficiently strong hyperpolarizing input. As a result, following the decay of IPSPs, some TC neurons rebound burst and re-excite TRN neurons (von Krosigk et al., 1993). By providing a common synaptic drive, inhibition might synchronize TC neuron activity during spindles (Rubin and Terman, 2000). This would be similar to the role of inhibition during gamma rhythms in hippocampal slices (Traub et al., 1996).

However, two recent observations suggest ways in which inhibition could also desynchronize thalamic activity. First, by hyperpolarizing neurons, inhibitory synaptic input might reveal differences in the neurons' voltage-dependent currents not apparent at rest. An example of this can be seen in a recording from a TRN neuron (Figure 1). A burst in this TRN neuron elicits return EPSPs after a long (> 200 msec) and highly variable latency (Fig 1). This suggests that after the arrival of an IPSP, the time it takes TC neurons to fire rebound bursts is long, relative to the decay of inhibitory synaptic currents (≈ 10-100 msec), and highly variable. The variability in the time that it takes different TC neurons to fire rebound bursts may reflect differences in the each cell's complement of voltage-dependent intrinsic currents.

Second, the main determinant of whether or not a TC neuron responds to an IPSP with a rebound burst seems to be the time when the next IPSP arrives. If an IPSP is followed by a window of time during which no other IPSPs arrive, then a rebound burst occurs. However, if a second IPSP arrives during this window, it "vetoes" the rebound burst. This is illustrated in Figure 2, which shows recordings from one TC neuron during two consecutive evoked oscillations. The initial pattern of IPSPs and their decay is almost identical in the two sweeps. However, in one sweep (black trace) a rebound burst (indicated by "*") occurs, whereas in the other (red trace), the arrival of a timely IPSP (indicated by "↑") prevents a rebound burst. In the latter sweep, the

neuron does eventually fire a rebound burst (indicated by "□"), but only when there is a sufficiently long interval between successive IPSPs.

Further confirmation for the ability $GABA_A$ receptor-mediated inhibition to veto rebound bursts comes from the simple experiment shown in Figure 3. Stimulation of corticothalamic fibers in internal capsule causes TRN neurons to burst, producing a large, slow IPSP in TC neurons which is dominated by $GABA_B$ receptor-mediated currents. In control conditions (black trace), the initial, evoked IPSP fails to elicit a rebound burst and is followed by an oscillatory pattern of faster, primarily $GABA_A$ receptor-mediated IPSPs. However, after application of the $GABA_A$ receptor antagonist picrotoxin (red trace), the evoked IPSP does elicit a rebound burst, although the amplitude and decay of the IPSP are unaffected. Thus, in control conditions, the rebound burst was prevented by the arrival of a fast IPSP (indicated by "↑").

Thus, there are at least three ways in which inhibition could affect the synchrony of thalamic oscillations. By eliciting rebound bursts, inhibitory synaptic currents provide a common, synchronizing drive to TC neurons. However, inhibition can also desynchronize oscillations in two ways. First, inhibition can elicit rebound firing at variable latencies (e.g. Figure 1), presumably by uncovering heterogeneous cellular properties. Second, firing by a subset of neurons may excite inhibitory neurons, which then veto firing by the remaining cells (e.g. Figures 2 and 3).

Preliminary simulations of a network, based on an earlier model (Sohal and Huguenard, 2002), containing 20 TRN neurons and 20 TC neurons confirm that inhibition can either synchronize or desynchronize thalamic oscillations. After simulating 10 seconds of activity, we smoothed and combined the spike trains from all TC neurons, and used the resulting time series of network activity to compute an autocorrelogram, from which we could measure the frequency and synchrony (peak-to-trough ratio).

Figure 4a shows autocorrelograms of network activity for several values of the $GABA_A$ receptor conductance on each TC neuron. Increasing the $GABA_A$ receptor conductance transforms a relatively desynchronized, spindle-like rhythm into a hypersynchronous epileptiform oscillation. This is illustrated by Figure 4b, which shows network activity (the sum of smoothed spike trains from all TC neurons) for two different values of the $GABA_A$ receptor conductance. Such a transformation is thought to underlie the emergence of absence seizures as a perversion of sleep spindles (Steriade et al., 1993).

Prolonging inhibition has more complex effects on network synchrony, as shown by Figure 4c, which plots autocorrelograms of network activity for several values of τ_{GABA}, the decay time constant for $GABA_A$ receptor-mediated currents in TC neurons. In most cases, prolonging inhibition, by increasing the decay time constant, increases synchrony. However, increasing τ_{GABA} from 24 msec to 32 msec decreases synchrony. Indeed, we have found that for values of τ_{GABA} around 30 msec, additional, small increases in τ_{GABA} decrease synchrony.

Thus, in simulations, inhibition can affect network synchrony in multiple ways: inhibition may provide a common, synchronizing influence throughout the network, it may reveal heterogeneous cellular properties, or it may veto the firing of some neurons. Moreover, the influence of inhibition on synchrony was much more pronounced when TC neurons had strongly

heterogeneous intrinsic properties. By regulating synchrony, inhibition may also contribute to transitions between different modes of oscillations, e.g. sleep spindles and absence seizures.

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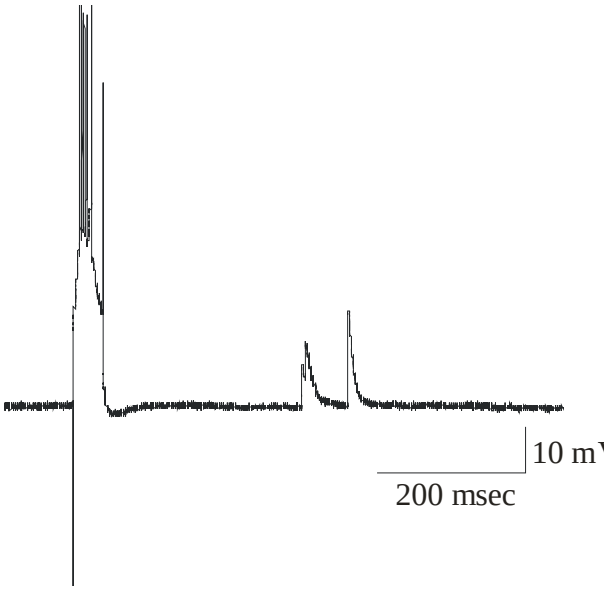

Figure 1

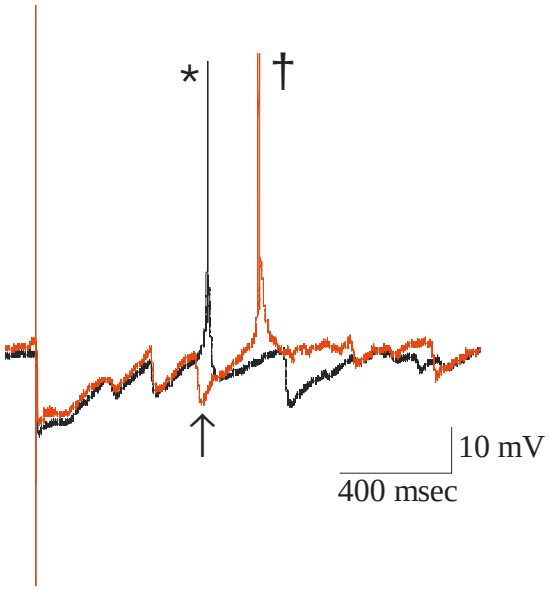

Figure 2

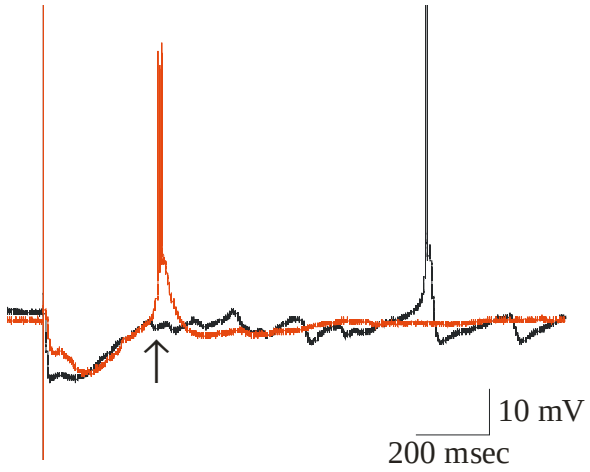

Figure 3

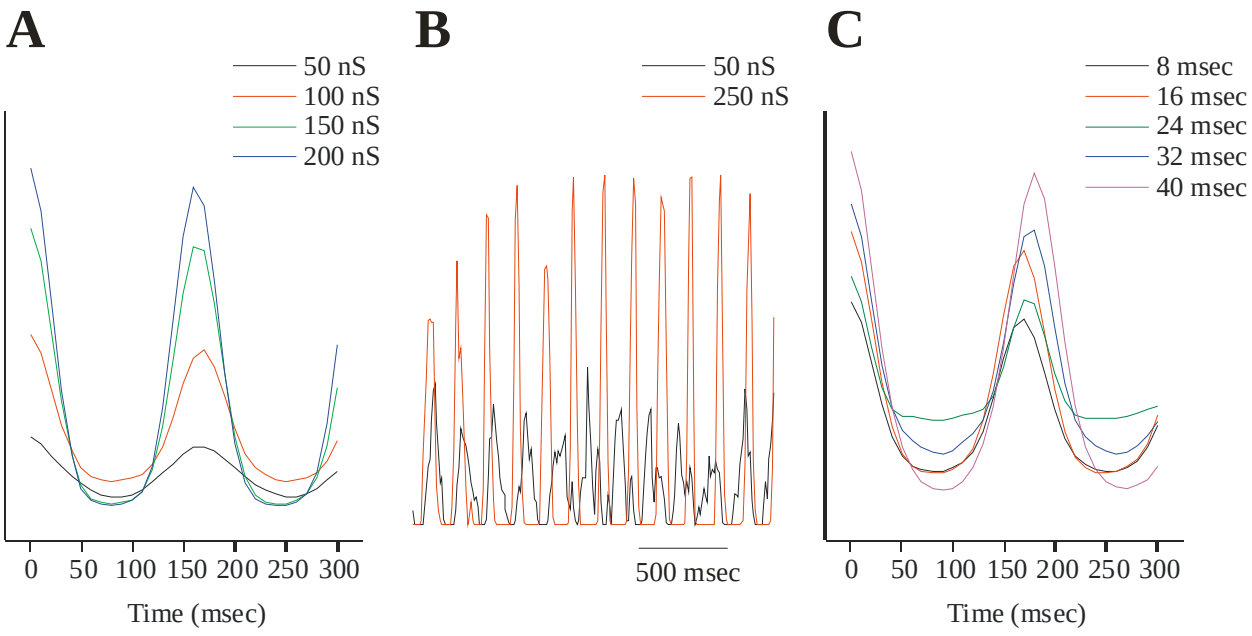

Figure 4