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The initiation of bursts in thalamic neurons and the cortical control of thalamic sensitivity

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Thalamic neurons generate high-frequency bursts of action potentials when a low-threshold (T-type) calcium current, located in soma and dendrites, becomes activated. Computational models were used to investigate the bursting properties of thalamic relay and reticular neurons. These two types of thalamic cells differ fundamentally in their ability to generate bursts following either excitatory or inhibitory events. Bursts generated with excitatory inputs in relay cells required a high degree of convergence from excitatory inputs, whereas moderate excitation drove burst discharges in reticular neurons from hyperpolarized levels. The opposite holds for inhibitory rebound bursts, which are more difficult to evoke in reticular neurons than in relay cells. The differences between the reticular neurons and thalamocortical neurons were due to different kinetics of the T-current, different electrotonic properties and different distribution patterns of the T-current in the two cell types. These properties enable the cortex to control the sensitivity of the thalamus to inputs and are also important for understanding states such as absence seizures.

Keywords: cortex; thalamus; oscillations; epilepsy; absence

1. INTRODUCTION

Thalamic circuits link peripheral sensory systems to the cerebral cortex through 'feed-forward' relay neurons. However, the major source of excitatory synapses in the thalamus is not afferent synapses from the periphery, but from the cerebral cortex itself (Guillery 1969; Jones 1985; Liu *et al.* 1995; Erisir *et al.* 1997*a*,*b*; Liu & Jones 1999). This is true not only for thalamic relay neurons, but also for the inhibitory cells of the thalamic reticularRE nucleus (Liu & Jones 1999). This massive cortical excitatory input suggests that the cortex might have a significant influence on the activity of the thalamus, but this possibility is often neglected.

Thalamic neurons display two distinct firing modes. Like most neurons, they can fire action potentials at a frequency proportional to the amplitude of depolarizing stimuli, when they are in their 'tonic' mode of firing. Thalamic neurons can also fire bursts of action potentials, which consist of a slow calcium-mediated spike, crowned by high-frequency action potentials. This 'burst' mode of firing is a consequence of an intrinsic voltage-dependent current, the low-threshold (T-type) calcium current (Llinás & Jahnsen 1982).

The thalamus generates powerful synchronized bursts of action potentials during slow-wave sleep, in contrast to the pattern of activity in alert animals, which is dominated by single-spike (tonic) firing (Livingstone & Hubel 1981; Steriade *et al.* 1990). There is, however, evidence for the presence of bursts in the thalamus of awake animals (Guido *et al.* 1992; Guido & Weyand 1995; Sherman 2001). The thalamic bursts may convey a special type of information in alert states, such as novelty detection (Sherman 2001). However, the occurrence of bursts is rare in the thalamus of aroused animals, and may instead signify that the animal is drowsy (Steriade 2001); this possibility is supported by observations that thalamic bursts are negatively correlated with attention (Weyand *et al.* 2001).

Intracellular recordings *in vivo* have found that the input resistance of thalamic neurons faithfully follows the state of the cortex during the different phases of anaesthetized states (Contreras *et al.* 1996), consistent with the massive excitatory input from the cortex. In particular, the cortex can modulate the firing mode of thalamic neurons through corticothalamic synapses. This 'descending' control of the thalamus (McCormick 1992) has, however, received little attention and it is at present unclear how the responsiveness of thalamic neurons to different inputs is modulated by cortical activity.

We use computational models to investigate how different types of synaptic afferents evoke burst or tonic responses in thalamic neurons. Different types of synapses are segregated in different locations on thalamic relay (Liu *et al.* 1995) and reticular neurons (Liu & Jones 1999) and differ in their quantal conductances (Golshani *et al.* 2001). We incorporated these details into models of morphologically reconstructed thalamic neurons in which synaptic inputs were simulated in different regions of the dendrites. We investigated how the responsiveness of thalamic neurons is affected by the types of synapse and is modulated by input activity.

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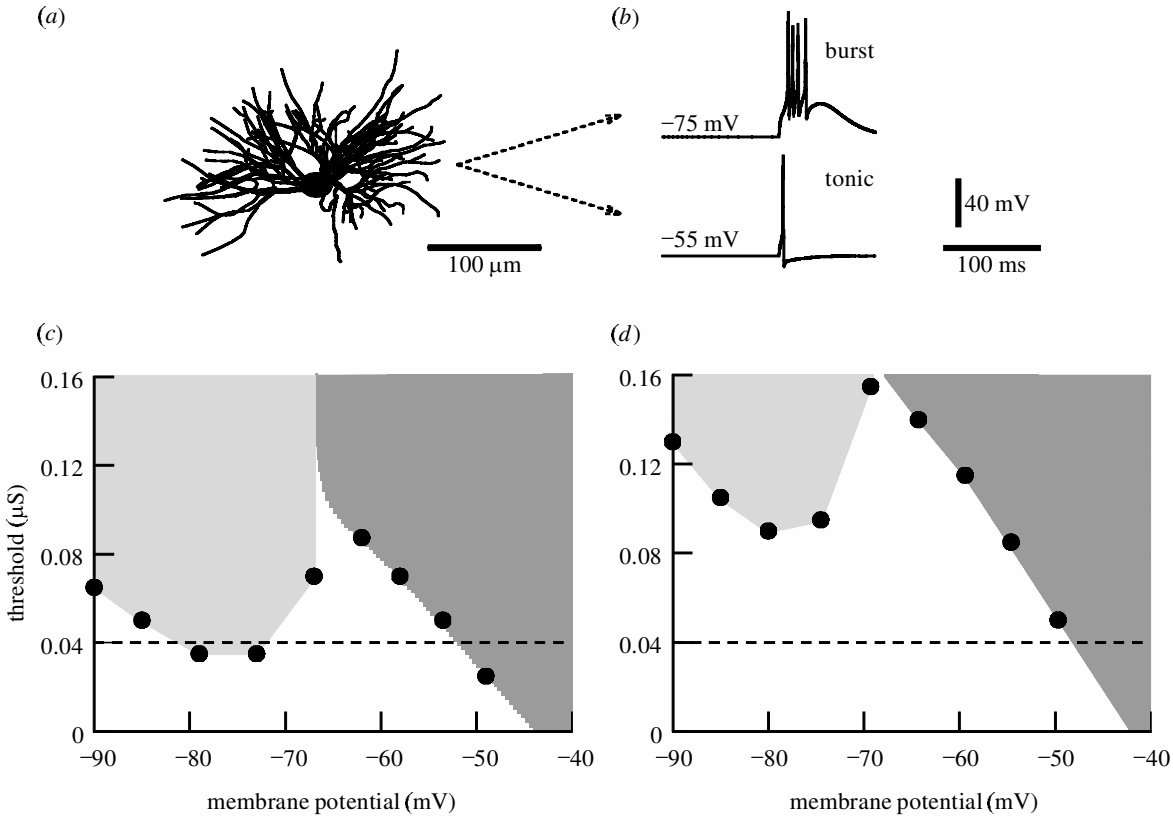

Figure 1. Burst and tonic responses to excitatory synaptic currents in model thalamic relay neurons. (*a*,*b*) Thalamic relay neuron from rat VB nucleus, reconstructed and incorporated into simulations (Destexhe *et al.* 1998*b*). Examples of burst and tonic responses to excitatory (AMPA-mediated) synaptic stimuli are shown at two different voltages. (*c*,*d*) Burst and tonic responses as a function of the membrane potential and stimulus amplitude. The model had high densities of T-current in proximal dendrites (see § 2) and the AMPA conductances were distributed in proximal dendrites (up to 40 μm from soma) and had a uniform conductance density. The threshold conductance (g_{AMPA}) for the excitatory synaptic current is indicated by filled circles. The shaded areas indicate burst (light grey) and tonic modes (dark grey). (*c*) Control: simulations using leak current estimated from whole-cell recordings *in vitro* (0.038 mS cm^{-2}). (*d*) High leak: the same simulations in the presence of a 'leaky' membrane (leak conductance of 0.15 mS cm^{-2}), closer to *in vivo* conditions. The horizontal dashed line represents an input of 0.04 μS, for which both burst and tonic responses are possible in control conditions. In leaky conditions, the burst region has shrunk, and the only possible output of this particular stimulus is a tonic discharge.

2. MATERIAL AND METHODS

The computational models were based on those in several previously published papers, in which the details of those models have been described (Destexhe *et al.* 1994, 1996, 1998*b*). All the models were simulated using the NEURON simulation environment (Hines & Carnevale 1997).

Computational models of thalamic relay and reticular neurons were based on cellular morphologies obtained in two previous studies (Destexhe *et al.* 1996, 1998*b*). These neurons (illustrated respectively in figures 1 and 3) were intracellularly recorded in slices from rat ventrobasal nucleus and stained with biocytin (Huguenard & Prince 1992). Their 3-D morphology was reconstructed using a computerized camera lucida system (Eutectic Electronics, Raleigh, NC, USA), and incorporated into NEURON to simulate the cable equations of these 3-D morphologies. Details of these methods can be found elsewhere (Destexhe *et al.* 1996, 1998*b*).

Passive properties were obtained by fitting the model to the passive responses obtained in voltage clamp from whole-cell recordings. Because the models and recordings corresponded to the same cellular morphology, this method allowed accurate estimation of the passive parameters. In some simulations, a high leak conductance was used to simulate synaptic background activity and the low input resistance typical of neurons recorded *in vivo*. This high leak conductance was of $g_{leak} = 0.15$ mS cm^{-2}.

Active currents (I_{Na}, I_{K-d}, I_T) were based on Hodgkin & Huxley (1952) type kinetic models (see equations and parameters in Destexhe *et al.* 1996, 1998*b*). The density of T-current in the dendrites of relay cells was estimated based on voltage-clamp recordings of the T-current in intact and dissociated cells (Destexhe *et al.* 1998*b*), as well as from direct measurements of channel activity in dendrites (Williams & Stuart 2000). A non-uniform distribution of T-channels was used (10.3×10^{-5} cm s^{-1} in soma, 20.6×10^{-5} cm s^{-1} in proximal dendrites less than 40 μm from soma and 2.5×10^{-5} cm s^{-1} elsewhere), similar to the pattern estimated by Williams & Stuart (2000). In thalamic reticular cells, the distribution of T-current was estimated from voltage-clamp recordings in intact and dissociated cells (see Destexhe *et al.* 1996 for details). These models with somatodendritic distributions of I_T were compared with models having 'soma-only' distributions, in which the same total amount of T-channels was located exclusively in the soma.

Synaptic inputs were simulated by kinetic models for glutamate AMPA, NMDA and $GABA_A$ receptor types (Destexhe *et al.* 1994). Synapses were located exclusively on the dendrites as described in the text. Synaptic inputs were distributed on the

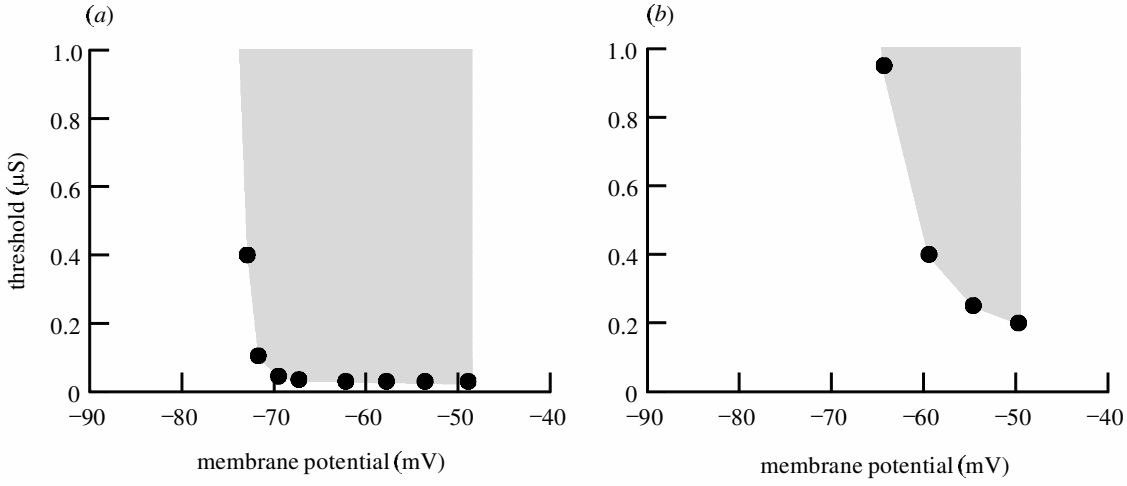

Figure 2. Rebound burst responses of model thalamic relay neurons. The same model and paradigms as in figure 1 were used, except that burst responses occurred at the offset of inhibitory synaptic currents ($GABA_A$-mediated). The responses are shown as a function of membrane potential and stimulus amplitude. The threshold conductance for the inhibitory synaptic current (g_{GABA_A}) is indicated by filled circles. (*a*) Control: burst responses (grey area) obtained with leak conductances of 0.038 mS cm^{-2}. (*b*) High leak: the same simulations in the presence of a higher leak conductance ($g_{leak} = 0.15$ mS cm^{-2}). In this case, the burst region (grey area) has shrunk, and more powerful IPSPs were needed to evoke rebound bursts.

dendrites according to the path distance from soma. For example, to localize cortical inputs in the distal third of thalamic relay cell dendrites, excitatory synapses were distributed in all dendritic segments with a path distance greater than 100 μm. The conductance of each synapse was scaled to the area of the dendritic segment, such that a constant density of conductance was located in the distal region (see text for conductance values). All excitatory conductance values refer to AMPA receptors; in some simulations the NMDA conductance was set to 25% of the AMPA conductance. Glutamate metabotropic receptors, which are present in corticothalamic synapses in relay cells (McCormick & von Krosigk 1993; Godwin *et al.* 1996), were not included.

3. RESULTS

We investigated the conditions for evoking bursts or tonic responses in the two types of thalamic cell, following either excitatory (AMPA-mediated) or inhibitory ($GABA_A$-mediated) synaptic inputs, in different regions of the dendrites.

(a) *Glutamatergic excitation of thalamic relay cells*

We used a morphologically reconstructed thalamic relay cell from the rat ventrobasal thalamus (Destexhe *et al.* 1998*b*) (figure 1*a*,*b*); passive and active properties were simulated based on whole-cell recordings (see § 2). We used a somato-dendritic distribution of the T-type Ca^{2+} current with highest density in proximal 'stem' dendrites, as found experimentally (Williams & Stuart 2000). Excitatory inputs were placed in the proximal region of dendrites (less than 40 μm from the soma) where most afferent synapses terminate (Jones 1985; Liu *et al.* 1995). Under these conditions, excitatory synapses were co-localized with most of the T-channels.

As expected from the voltage dependence of I_T, the genesis of bursts by excitatory inputs strongly depended on the resting membrane potential, which must be sufficiently negative for I_T to deinactivate, triggering the burst discharges. At more depolarized resting levels, excitatory inputs produced tonic (single-spike or multiple-spike) responses. Figure 1*b* shows representative examples of burst and tonic discharges obtained from excitatory inputs in relay cells.

Figure 1*c*,*d* shows the spectrum of burst and tonic modes obtained as a function of the resting level and the amplitude of the excitatory stimulus. Under control conditions (leak conductance estimated from whole-cell recordings *in vitro*), bursts could only be evoked below −65 mV and required a total conductance of at least 0.035 μS (figure 1*c*). With high leak conductance (corresponding to *in vivo* conditions), the burst region (light grey in figure 1*c*,*d*) shrank, though the tonic region (dark grey) was affected to a lesser extent. Under these conditions, the conductance threshold for evoking bursts was of 0.09 μS (figure 1*d*). For inputs below that conductance, the only possible output of the cell is a tonic response (see horizontal dashed line in figure 1).

Similar conclusions were reached using excitatory inputs localized in the distal third of relay cell dendrites, similar to the pattern of localization of cortical synapses in these cells (Liu *et al.* 1995). The spectrum of burst and tonic modes in control conditions was almost indistinguishable from that of figure 1*c*, but in leaky conditions, the cell was slightly less sensitive (threshold EPSP for burst generation was 0.095 μS). Focal inputs, restricted to one or a few dendritic branches, produced similar results. The inclusion of NMDA conductances did not qualitatively change this pattern. Using a soma-only distribution of I_T led to a range of burst and tonic modes that were indistinguishable from those obtained with dendritic I_T (not shown), suggesting that the dendritic localization of T-channels has no significant effect on the sensitivity of relay cells to burst generation. By contrast, the locations of T-channels were important for determining the responsiveness of thalamic reticular neurons (see next section).

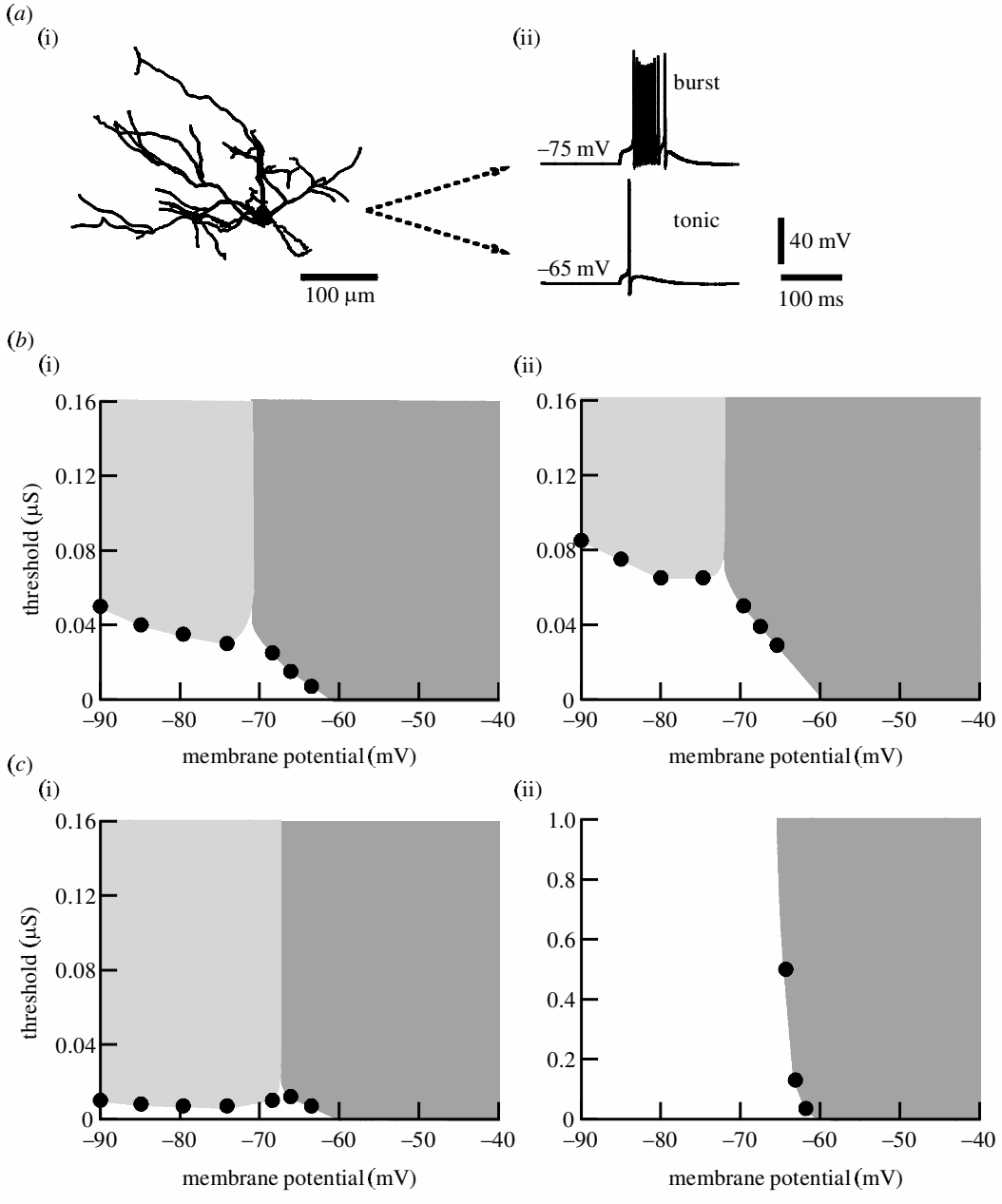

Figure 3. Burst and tonic responses to excitatory synaptic currents in model thalamic reticular neurons. (*a*(i),(ii)) Thalamic reticular neuron from rat VB nucleus, reconstructed and incorporated into simulations (Destexhe *et al.* 1996). The model had high densities of T-current in dendrites. Examples of burst and tonic responses to excitatory (AMPA-mediated) synaptic stimuli are shown at two different voltages. (*b*) Responses obtained when excitatory conductances were distributed throughout the dendrites with uniform conductance density. As in figure 1, burst and tonic responses are shown by grey regions (light grey for burst and dark grey for tonic), as a function of the membrane potential and stimulus amplitude. The threshold conductance (g_{AMPA}) for evoking a response is indicated by filled circles. (*c*) Responses obtained when excitatory synapses were focally distributed in 'hot spots' or in restricted regions of dendrites (in this case, distal dendrites at more than 250 μm from soma). The AMPA conductance density was always uniform in a given dendritic region. For both (*b*) and (*c*), the responses are indicated for two different leak conductances: (i) control; leak conductance of $g_{leak} = 0.05$ mS cm^{-2} estimated from whole-cell recordings. (ii) High leak; higher leak conductance of $g_{leak} = 0.15$ mS cm^{-2}. The genesis of bursts was always more sensitive to EPSPs for focal inputs (*c*(i)), but was often very reduced or totally absent in a leaky membrane (*c*(ii); note change of scale).

(b) *Inhibitory rebound bursts in thalamic relay cells*

The dense GABAergic innervation in thalamic relay cells from the thalamic reticular nucleus (Jones 1985) can elicit inhibitory-rebound bursts of action potentials through deinactivation of I_T. There is evidence that inhibitory synapses are distributed all through the dendrites of relay cells (Liu *et al.* 1995; Kim *et al.* 1997). To investigate how these dendritic conductances affect rebound burst generation, we used a model with dendritically located I_T (see above), together with a uniform distribution of $GABA_A$ receptors on the dendrites (see § 2). As expected from the voltage dependence of I_T, and the negative reversal potential of fast inhibition in relay cells (−95 mV in Ulrich & Huguenard 1997), rebound bursts can only be obtained within a given range of membrane potentials and

IPSP amplitudes, as shown in figure 2. Thalamic relay cells were generally sensitive to IPSPs of moderate amplitude, with a threshold conductance of 0.03 μS for generating inhibitory rebound bursts (figure 2*a*). In the presence of stronger leak currents, mimicking *in vivo* conditions, the threshold for inhibitory rebound bursts was higher (0.2 μS; figure 2*b*).

Similar conclusions were obtained when the T-channels were located exclusively in the soma. The inhibitory rebound burst region was identical to figure 2*a*. In leaky conditions, the cell was slightly more sensitive at hyperpolarized membrane potentials (not shown), but had the same threshold IPSP for rebound burst generation (0.2 μS).

(c) *Glutamatergic excitation of thalamic reticular cells*

Simulations were performed with a morphologically reconstructed neuron from the rat ventrobasal sector of the thalamic reticular nucleus (Destexhe *et al.* 1996) (figure 3*a*). Passive and active properties were simulated based on whole-cell recordings (see § 2). The somato-dendritic distribution of the T-type Ca^{2+} current followed previous estimates from voltage- and current-clamp recordings (Destexhe *et al.* 1996), in which the highest density was in the distal dendrites.

Corticothalamic synapses are the dominant type on thalamic neurons (Liu & Jones 1999) and are only weakly segregated on the dendrites of reticular neurons. In proximal dendrites, *ca*. 50% of the synapses are corticothalamic, 30–40% are from thalamic relay cells and 10–25% are GABAergic. In distal dendrites, there is a higher density of cortical synapses (60–65%) compared with the other types (20% and 15%, respectively; Liu & Jones 1999). We simulated excitatory synapses with three distribution patterns: a uniform dendritic distribution, focal 'hot spot' distributions or distal dendritic distribution of excitatory synapses (greater than 250 μm from the soma).

Thalamic reticular neurons responded to excitatory stimuli by producing either burst or tonic responses (figure 3*a*(ii)). For uniformly distributed excitatory synapses, the spectrum of burst and tonic mode followed the voltage dependence of I_T (figure 3*b*). Under control conditions (leak current estimated from whole-cell recordings *in vitro*), the threshold for burst generation was 0.03 μS (figure 3*b*(i)), slightly lower than that of relay cells in the same conditions. In the presence of high leak conductances, simulating *in vivo* conditions, the burst region shrank (light grey in figure 3*b*(ii)) and had a threshold of 0.065 μS. Thus, the spectra of burst and tonic modes for distributed excitatory conductances in dendrites are qualitatively similar to those obtained in relay cells (compare with figure 1). The reticular neuron was, however, slightly more sensitive to burst generation.

Responses from reticular neurons were different when excitatory synapses were localized more focally, either in 'hot spots' (in single, or several, dendritic branches), or on distal dendrites. Burst generation was remarkably sensitive in control conditions (figure 3*c*(i)), with a threshold AMPA conductance of 0.007 μS for excitatory synapses located in distal dendrites (greater than 250 μm from the soma), about one order of magnitude lower than for distributed excitation. In the presence of strong leak conductances, burst generation was much more affected, and it was not possible to evoke bursts by excitation, even for very high excitatory conductances (figure 3*c*(ii)). Tonic firing activity, however, did not show such dramatic changes. Qualitatively similar patterns were observed for 'hot spots' of AMPA synapses localized in single dendritic branches, provided these branches were not proximal to the soma (not shown).

Unlike the results from relay cells, the responses of reticular neurons were greatly influenced by the somatodendritic localization pattern of I_T. With a 'soma-only' distribution of I_T, burst generation was always less sensitive to excitatory conductances (threshold AMPA conductance of 0.035 μS for control, and 0.07 μS for high leak). For distal dendritic localization (or hot spots), this effect was more dramatic, with a threshold AMPA conductance of 1.5 μS in control conditions (compared with 0.007 μS with dendritic I_T), showing that the high sensitivity to burst generation is dependent on the dendritic localization of the T-current.

(d) *Inhibitory rebound bursts in thalamic reticular cells*

We next investigated the conditions for rebound burst generation in thalamic reticular neurons. There is an approximately even distribution of GABAergic synapses in the different parts of the dendritic tree (Liu & Jones 1999). We simulated the genesis of rebound bursts using inhibitory ($GABA_A$-mediated) synapses distributed uniformly in the dendrites of the reconstructed reticular neuron, together with somatodendritic distributions of the T-current (see above). Rebound bursts in thalamic reticular cells depended on the membrane potential and the magnitude of the GABAergic conductance. The range for rebound burst generation is shown in figure 4. The threshold $GABA_A$ conductance for inhibitory rebound burst was of 0.015 μS with leak current estimated from whole-cell recordings *in vitro* (figure 4*a*). In the presence of stronger leak currents, mimicking *in vivo* conditions, the burst region narrowed (figure 4*b*; threshold conductance of 0.14 μS). Compared with relay cells, thalamic reticular cells were more sensitive to rebound burst generation at depolarized membrane potentials, but they were much less sensitive at hyperpolarized levels (not shown). Overall, the region where rebound bursts were possible was smaller in reticular neurons compared with relay cells (compare figures 2 and 4).

The sensitivity of rebound burst generation depended on the somatodendritic pattern of distribution of I_T. Rebound bursts required larger GABAergic conductances when I_T was localized exclusively in the soma: the threshold $GABA_A$ conductances were 0.02 μS (control conditions) and 0.2 μS (in the presence of strong leak currents). In contrast to bursts generated by excitatory inputs (see above), focal 'hot spot' inhibitory input made no dramatic difference in threshold compared with distributed patterns; however, distal patterns of GABAergic synapse localization gave a rebound burst with small apparent IPSP amplitudes at the soma, even though the conductance threshold was similar to uniformly distributed synapses (not shown). This can be explained by the strong voltage attenuation in these neurons (Destexhe *et al.* 1996). In this case, the GABAergic IPSP experienced a strong passive attenuation because of its distal localization,

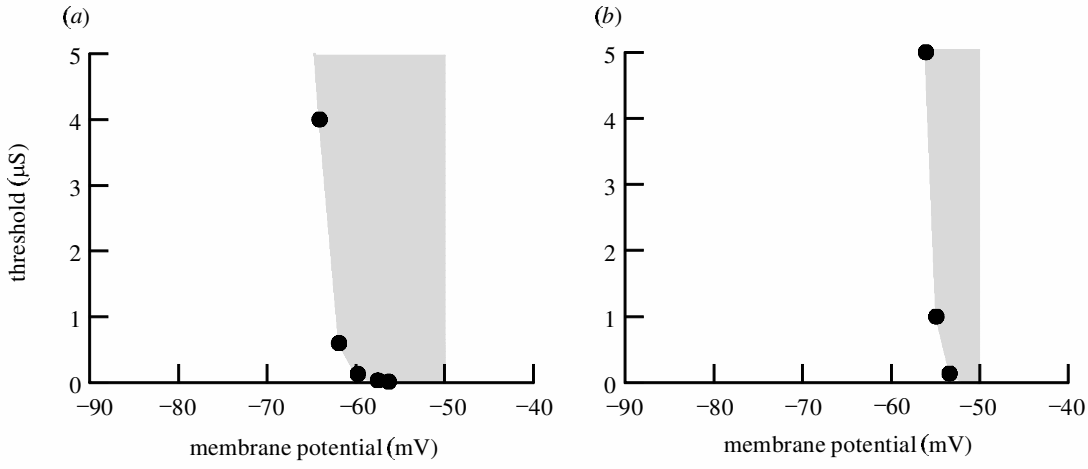

Figure 4. Rebound burst responses in model thalamic reticular neurons. (*a*) Control: burst responses (grey area) obtained at the offset of inhibitory synaptic currents ($GABA_A$-mediated), as a function of the membrane potential. The threshold conductance for the inhibitory synaptic current (g_{GABA_A}) is indicated by filled circles. (*b*) High leak: the same simulation in the presence of a higher leak conductance ($g_{leak} = 0.15$ mS cm^{-2}). In this case, the burst region has shrunk, and more powerful IPSPs were needed to evoke rebound bursts. In comparison with relay cells, the burst region was always smaller and larger IPSP conductances were generally needed to evoke rebound bursts (compare with figure 2).

but the low-threshold spike actively propagated down to the soma due to dendritic I_T channels.

4. DISCUSSION

The above simulations for how excitatory and inhibitory synaptic stimuli affect the firing mode of thalamic relay and reticular neurons reveal differences between them that could have functional implications. The results of these computational models for thalamic cells are used here to make quantitative predictions that can be tested experimentally.

(a) *The convergence requirements to evoke bursts in thalamic neurons*

The threshold for burst generation by excitatory synapses is surprisingly high in thalamic relay cells. The threshold conductance was at least 0.035 μS, and could be as high as 0.09 μS in the presence of strong leak currents. Given that the quantal amplitude of afferent synapses in relay cells has been estimated to be 100–150 pS (Paulsen & Heggelund 1994, 1996), these thresholds predict that a convergence of synaptic release from 230–350 sites is necessary to evoke bursts in relay cells by excitation. The required convergence is even stricter under *in vivo* conditions (high leak conductance), where at least 600–900 simultaneously release sites would be needed. Similar conclusions also apply to cortical synapses, which have a quantal conductance of 103 ± 25 pS (Golshani *et al.* 2001).

In the visual thalamus, the evoked conductance from a single retinal afferent has been estimated to be 0.6–3.4 nS (1.7 nS on average), which corresponds to 4–27 quantal events (Paulsen & Heggelund 1994). This would suggest that the simultaneous release of all terminal sites from 8 to 87 retinal axons are required to evoke bursts in relay cells (from 22 to 220 under *in vivo* conditions). However, a single retinal axon may create a large number of synaptic terminals onto the same relay neuron, forming a significant proportion of all of its retinal synapses (Hamos *et al.* 1987). It is therefore possible that the convergence of a relatively small number of afferent axons could evoke bursts, which would support the notion that bursts are easily triggered by afferent excitatory synapses. More precise measurements of the number of synaptic terminals from single axons are needed.

Excitatory inputs on thalamic reticular neurons can also generate bursts. The threshold conductance strongly depended on the distribution pattern of synapses in dendrites. For uniform dendritic excitation, the threshold was *ca.* 0.03 μS and increased to 0.065 μS under *in vivo* conditions, somewhat weaker than for relay cells. Given that the quantal conductance of glutamatergic synapses on reticular neurons is *ca.* 266 ± 48 pS (Golshani *et al.* 2001), these threshold values predict a convergence of approximately 113 excitatory release sites in control conditions and approximately 244 release sites under *in vivo* conditions. However, for focal 'hot spot' type distributions, the threshold was much lower, 0.007 μS, corresponding to approximately 26 release sites, but it was not possible to evoke bursts under *in vivo* conditions.

Burst generation can also occur in rebound to fast ($GABA_A$-mediated) inhibitory events. In relay cells, the threshold for rebound burst generation was *ca.* 0.03 μS, and increased to 0.2 μS under *in vivo* conditions. For an estimated quantal conductance of $GABA_A$ synapses of 300 pS (Cox *et al.* 1997; Le Feuvre *et al.* 1997; Ulrich & Huguenard 1997), the threshold conductances predict that between 100 (control) and 660 (*in vivo*) GABAergic synapses must be co-activated to elicit a rebound burst in thalamic relay cells. Morphological studies indicate that a single axon from reticular neurons establish, on average, 60 synapses on the same postsynaptic relay cell (Kim *et al.* 1997). Therefore, a relatively low convergence of between 2 and 10 reticular cells may securely evoke rebound bursts in thalamic relay neurons. If reticular neurons fire bursts of several action potentials, a burst in a single reticular neuron should be large enough to evoke a rebound burst in a relay cell, as was indeed observed *in vitro* (Bal & McCormick 1996).

$GABA_A$-mediated rebound bursts in reticular neurons generally required stronger conductances, and were found over a narrower range of membrane potentials compared with the range in relay cells (see figures 2 and 4). The high sensitivity to focal excitatory synaptic activation (figure 3*c*) was not observed for GABAergic inputs. Because there is no morphological evidence for a large convergence of inhibitory contacts between reticular neurons (see Pinault *et al.* 1995), inhibitory rebound interactions between reticular neurons presumably require a high level of synchrony within the reticular nucleus. However, local dendritic interactions through dendro-dendritic GABAergic synapses and dendritic T-channels (Mulle *et al.* 1986) may provide the basis of mutual inhibitory-rebound interactions between reticular neurons. More precise estimates of the conductances and numbers of these synapses, as well as the role of other types of coupling (such as gap junctions; see Landisman *et al.* 2002), are needed to examine the likelihood of mutual rebound interactions between reticular neurons.

The high sensitivity of reticular neurons to burst generation by focal or distal excitation (figure 3*c*) depends on the presence of the T-current in the distal dendrites. This sensitivity was not observed in relay neurons, in part because they are electrotonically more compact (the maximal electrotonic length of relay cells was 0.34, compared with 2.7 in reticular neurons; see Destexhe *et al.* 1996, 1998*b*), but also because of differences in the voltage dependence of the T-current in the two cell types: reticular T-channels are slower and have a less steep activation range compared with relay cells (Huguenard & Prince 1992). These differences may also explain the narrow range of voltages within which rebound bursts can be activated in reticular neurons (see figures 2 and 4).

(b) *Functional consequences*

Our simulations reveal a critical difference between tonic and burst firing in thalamic neurons (figures 1 and 3): tonic (single-spike) firing can be evoked by arbitrarily small excitatory inputs, depending on the proximity of the resting level of the cell to the firing threshold, but bursts of action potentials always require powerful inputs and they only occur if thalamic neurons rest at a sufficiently hyperpolarized membrane potential. The models also suggest that cortical activity, by evoking increased tonic conductance in relay cells, can counteract burst genesis and further enhance these differences, effectively favouring the tonic mode (figure 5*a*). Thus, relay cells are more likely to generate bursts when there is a powerful afferent excitation occurring under low-activity conditions, consistent with the burst mode as a strong filter of afferent information (McCormick & Feeser 1990). These results also support the view that bursts may be a 'wake-up call' signal during drowsiness or inattentive states (Sherman 2001), though it is not clear how the cortex would distinguish these 'wake-up' bursts from bursts occurring spontaneously (or in an oscillation) during states of low vigilance.

Reticular neurons generate bursts when they are excited from a hyperpolarized level and are exquisitely sensitive to excitatory inputs localized in dendrites, in agreement with a previous study (Destexhe 2000). Given the high sensitivity of relay cells to IPSPs, bursts in reticular neurons

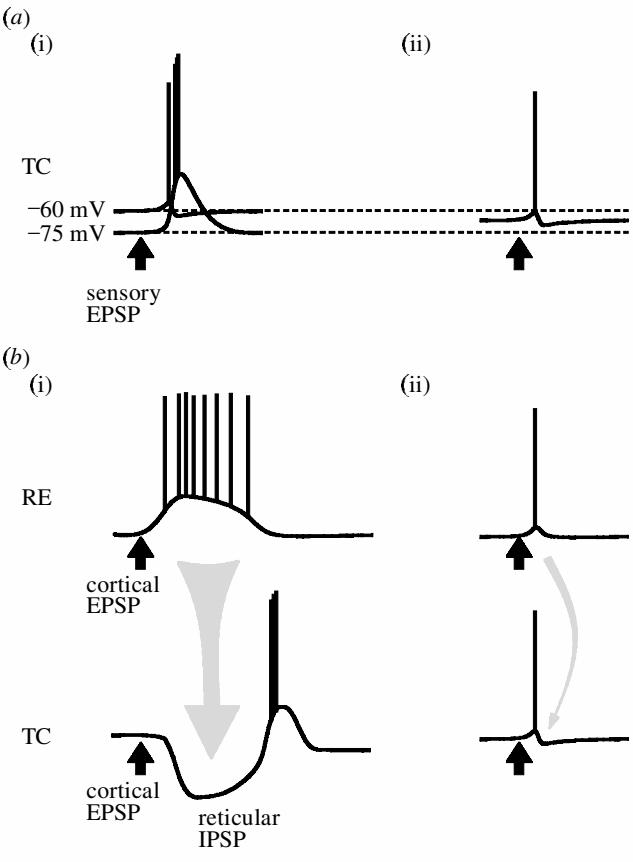

Figure 5. Model predictions in terms of controlling the sensitivity of thalamic neurons. (*a*) Responses to afferent (sensory) synapses. (i) Quiescent: bursts can be evoked by sensory EPSPs in TC relay cells only at hyperpolarized membrane potentials and for sufficiently strong inputs. (ii) Active: under *in vivo*-like conditions, the cortical activity exerts a tonic increase of conductance in thalamic neurons. Burst genesis requires exceptionally strong inputs, and the dominant responses are single-spike tonic discharges at all voltages. (*b*) Responses to cortical synapses. (i) Quiescent: the burst response of thalamic reticular neurons is sensitive to cortical EPSPs. These bursts generate a strong feed-forward IPSP that dominates the cortical EPSP in TC cells. In this case, the cortex recruits relay cells through massive inhibition, and securely evokes an IPSP-rebound sequence in relay cells. (ii) Active: under *in vivo*-like conditions, the increase of conductance due to cortical activity greatly reduces the sensitivity of both cell types, and counteracts burst firing, so that the tonic-firing mode dominates. In this case, the cortex should recruit thalamic relay cells through dominant excitation, therefore favouring the relay of information. Abbreviation: RE, thalamic reticular.

are likely to evoke rebound bursts in relay cells through rebound inhibition. Thus, the connectivity and properties of relay and reticular neurons predispose them to mutually recruit each other through bursts of action potentials. Cortical feedback provides an alternative route to evoke bursts in reticular neurons, which in turn recruits relay cells through powerful IPSPs (figure 5*b*(i)). This 'inhibitory dominance' of corticothalamic interactions may also explain how the cortex organizes large-scale synchrony during slow-wave sleep (Destexhe *et al.* 1998*a*) and how the TC system generates pathological states such as absence seizures (reviewed in Destexhe & Sejnowski 2001). However, if both cell types are in the tonic mode,

the cortical feedback may become 'excitatory-dominant' (figure 5*b*(ii); Destexhe 2000). Our models therefore suggest that whether corticothalamic feedback is excitatory or inhibitory depends entirely on whether the thalamic circuits are, respectively, in a tonic or bursting state; this implies that the impact of the cortex on the thalamus is regulated by neuromodulators, which can shift the thalamus between these two states.

Cortical activity can regulate the state of the thalamus with greater spatial and temporal precision than is possible with diffuse neuromodulators. Because of dendritic T-currents, the responsiveness of reticular neurons is strongly modulated by background activity (especially for focal dendritic inputs (figure 3*b*) from cortical and neuromodulatory inputs. When the cortex is less active or silent, the requirements for burst generation are less restrictive and, as a consequence, bursting interactions are favoured in thalamic circuits (figure 5*b*(i)). By contrast, sustained cortical drive imposes strong restrictions on burst generation, and thus promotes tonic firing (figure 5*b*(ii)). Through this mechanism, cortical inputs can switch the thalamus from burst to tonic mode in a few milliseconds. Thus, the responsiveness of thalamic circuits to sensory signals arising from the periphery is controlled by cortical inputs interacting with different types of voltage-dependent and synaptic conductances distributed non-homogeneously in the dendrites. Closely coupled experiments and computational models could provide a deeper understanding of how these mechanisms interact to regulate the flow of information into the cortex and between cortical areas.

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GLOSSARY

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
EPSP: excitatory postsynaptic potential
GABA: γ-aminobutyric acid
$GABA_A$: γ-aminobutyric acid type-A
IPSP: inhibitory postsynaptic potential
NMDA: *N*-methyl-D-aspartate
TC: thalamocortical