Phil. Trans. Roy. Soc. Lond. Series B
(manuscript submitted on April 30, 2002)

THE INITIATION OF BURSTS IN THALAMIC NEURONS AND THE CORTICAL CONTROL OF THALAMIC SENSITIVITY

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SUMMARY

Thalamic neurons generate high-frequency bursts of action potentials due to the presence of a low-threshold (T-type) calcium current. We used computational models to investigate the genesis of bursting in thalamic relay and reticular neurons, with most of the T-type current located in the dendrites. These two types of thalamic cells are fundamentally different 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. The opposite holds for inhibitory rebound bursts, which are more difficult to obtain in reticular neurons than in relay cells. These differences 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 of thalamic circuits and the thalamocortical system enable the cortex to control the sensitivity of the thalamus to inputs and also influence pathological states such as absence seizures.

INTRODUCTION

Thalamic circuits link peripheral sensory systems to the cerebral cortex through "feedforward" relay neurons. However, the major source of excitatory synapses in the thalamus are not afferent synapses from the periphery, but from the cerebral cortex itself (Guillery 1969; Jones 1985; Liu et al. 1995; Erisir et al. 1997a, 1997b; Liu & Jones 1999). This is true not only for thalamic relay neurons, but as well for the inhibitory cells of the thalamic reticular nucleus (Liu & Jones 1999). This massive cortical excitatory input suggests that the cortex might have a determinant 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 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 follow the state of the cortex during the different phases of anesthetized 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.

In this paper, 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 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 how this responsiveness is modulated by activity.

MATERIALS AND METHODS

The computational models were based on those in several previously published papers, in which the details of the models have been described (Destexhe et al. 1994, 1996, 1998b). 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, 1998b). These neurons (illustrated respectively in Figs. 1 and 3) were intracellularly recorded in slices from rat ventrobasal nucleus and stained with biocytin (Huguenard & Prince 1992). Their morphology was reconstructed in 3-D 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. All details about these methods can be found elsewhere (Destexhe et al. 1996, 1998b).

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_{Kd}, I_T) were based on Hodgkin & Huxley (1952) type kinetic models (see equations and parameters in Destexhe et al. 1996, 1998b). 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. 1998b) 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 in soma, 20.6 10^{-5} cm/s in proximal dendrites <40 μm from soma, and 2.5 10^{-5} cm/s 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 α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and γ-aminobutyric acid type-A ($GABA_A$) receptor types (Destexhe et al. 1994). Synapses were located exclusively in the dendrites as described in the text. Synaptic inputs were distributed on the 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 path distance >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.

RESULTS

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

Glutamatergic excitation of thalamic relay cells

We used a morphologically-reconstructed thalamic relay cell from rat ventrobasal thalamus (Destexhe et al. 1998b) (Fig. 1, top scheme), in which passive and active properties were simulated based on whole-cell recordings (see Methods). 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 ($<$40 μm from the soma) where most afferent synapses terminate (Jones 1985; Liu & Jones 1995). Under these conditions, excitatory synapses were co-localized with most of the T-channels.

As expected from the voltage-dependent properties 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 (top) shows representative examples of burst and tonic discharges obtained from excitatory inputs in relay cells.

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

Similar conclusions were reached by using distal excitatory inputs, localized in the distal third of relay cell dendrites, similar to the pattern of localization of cortical synapses in these cells (Liu & Jones 1995). The spectrum of burst and tonic modes in control conditions was nearly indistinguishable from that of Fig. 1 (*Control*), 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 few dendritic branches, also gave similar results. Inclusion of NMDA conductances did not qualitatively change this pattern. Using a soma-only distribution of I_T led to spectra 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. However, different conclusions were reached for thalamic reticular neurons (see below).

Inhibitory rebound bursts in thalamic relay cells

Thalamic relay cells receive a dense GABAergic innervation from the thalamic reticular nucleus (Jones 1985), which can lead to 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 & Jones 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 in the dendrites (see Methods). 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 bursting activity can only be obtained within a given range of membrane potentials and IPSP amplitudes, as shown in Fig. 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 (Fig. 2, *Control*). In the presence of stronger leak currents, mimicking *in vivo* conditions, the threshold for inhibitory rebound bursts was higher (0.2 μS; Fig. 2, *High leak*).

Similar conclusions were obtained by locating T-channels exclusively in the soma. The inhibitory

rebound burst region was identical to Fig. 2 (*Control*). 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).

Glutamatergic excitation of thalamic reticular cells

We used a morphologically-reconstructed neuron from the rat ventrobasal sector of the thalamic reticular nucleus (Destexhe et al. 1996) (Fig. 3, top scheme). Passive and active properties were simulated based on whole-cell recordings (see Methods). There was a somato-dendritic distribution of the T-type Ca^{2+} current with the highest density in distal dendrites, as estimated previously from voltage- and current-clamp recordings (Destexhe et al. 1996).

Corticothalamic synapses are the dominant type on thalamic neurons (Liu & Jones 1999) and are only weak segregated on the dendrites of reticular neurons. In proximal dendrites, approximately 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 to the other types (20% and 15%, respectively; Liu & Jones 1999). We simulated excitatory synapses according to three distribution patterns: a uniform dendritic distribution, focal "hot-spot" distributions, or distal dendritic distribution of excitatory synapses ($>$250 μm from the soma).

Thalamic reticular neurons responded to excitatory stimuli by producing either burst or tonic responses (Fig. 3, top). For uniformly distributed excitatory synapses, the spectrum of burst and tonic mode followed the voltage-dependence of I_T (Fig. 3A). Under control conditions (leak current estimated from whole-cell recordings *in vitro*), the threshold for burst generation was 0.03 μS (Fig. 3A, *Control*), 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 gray in Fig. 3A, *High leak*) 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 Fig. 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 in distal dendrites. Burst generation was remarkably sensitive in control conditions (Fig. 3B, *Control*), with a threshold AMPA conductance of 0.007 μS for excitatory synapses located in distal dendrites ($>$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 (Fig. 2B, *High leak*). 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 somatodendritic pattern of localization of I_T was highly influential in reticular neurons. 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.

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 considered the genesis of rebound bursts by 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 Fig. 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* (Fig. 4, *Control*). In the presence of stronger leak currents, mimicking *in vivo* conditions, the burst region narrowed (Fig. 4, *High leak*; threshold conductance of 0.14 μS). Compared to 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 were rebound bursts were possible was smaller in reticular neurons compared to relay cells (compare Figs. 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 $GABA_A$ conductance was 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" of inhibitory input made no dramatic difference in threshold compared to 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, but the low-threshold spike actively propagated down to the soma due to dendritic I_T channels.

DISCUSSION

We discuss here the implications of differences revealed by computational models for how excitatory and inhibitory synaptic stimuli affect the firing mode of thalamic cells and we make quantitative predictions which could be tested experimentally.

The convergence requirements to evoke bursts in thalamic neurons

We found that 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

was estimated to be about 100-150 pS (Paulsen & Heggelund 1994, 1996), these thresholds predict that a convergence of 230-350 release sites is necessary to evoke bursts in relay cells by excitation. The required convergence is even more severe under *in vivo* conditions (high leak conductance), in which case at least 600-900 simultaneously releasing 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 was estimated to be 0.6 to 3.4 nS (1.7 nS on average), which represents from 4 to 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 make 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, it was approximately 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 approximately 266 ± 48 pS (Golshani et al. 2001), these threshold values predict a convergence of about 113 excitatory releasing sites in control conditions, and about 244 releasing sites under *in vivo* conditions. However, for focal "hot-spot" type of distributions, the threshold was much lower, 0.007 μS, corresponding to approximately 26 releasing sites, but it was not possible to evoke bursts under *in vivo* conditions.

Burst generation was also investigated in rebound to fast ($GABA_A$-mediated) inhibitory events. In relay cells, the threshold for rebound burst generation was approximately 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 to the range in relay cells (see Figs. 2 and 4). The high sensitivity to focal excitatory synaptic activation (Fig. 3B) 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 (Fig. 3B) 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 to 2.7 in reticular neurons; see Destexhe et al. 1996, 1998b), 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 to relay cells (Huguenard and Prince, 1992). These differences may also explain the narrow range of voltages within which rebound bursts can be activated in reticular neurons (see Figs. 2 and 4).

Functional consequences

Sensory signals can evoke bursts in relay cells if there is sufficiently high convergence of afferents, as discussed above. In addition, relay cells must rest at a sufficiently hyperpolarized membrane potential (Fig. 1; see also Fig. 5A, *Quiescent*). Cortical activity, by evoking a tonic conductance increase in relay cells, can counteract burst genesis and favor the tonic mode (Fig. 5A, *Active*). Thus relay cells are 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 and Feeser, 1990). It also supports the view that bursts may be a "wake-up call" signal during drowsiness or inattentive states (Sherman 2001), although 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 are likely to evoke rebound bursts in relay cells through rebound inhibition. Thus, relay and reticular neurons seem to be optimally wired to mutually recruit each other through bursts of action potentials. Cortical feedback can also evoke bursts in reticular neurons, which in turn recruit relay cells through powerful IPSPs (Fig. 5B, *Quiescent*). This "inhibitory dominance" of corticothalamic interactions was postulated by computational models as a mechanism to explain how the cortex organizes large-scale synchrony during sleep states (Destexhe et al. 1998a) and how the thalamocortocal 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" (Fig. 5B, *Active*; Destexhe, 2000). Our models therefore suggest that the nature (excitatory or inhibitory) of corticothalamic feedback is entirely dependent on the state (tonic or bursting) of thalamic circuits.

Models also point to a determinant role of the activity of the cortex in determining the state of the thalamus. Because of dendritic T-currents, the responsiveness of reticular neurons is strongly modulated by background activity (especially for focal dendritic inputs (Fig. 3B)) from cortical and neuromodulatory inputs. When the cortex is less active or silent, bursting interactions are favored in thalamic circuits (Fig. 5B, *Quiescent*). In contrast, sustained cortical drive promotes tonic firing

(Fig. 5B, *Active*), since the requirements for burst generation are more tight. Cortical inputs can therefore switch the thalamus from burst to tonic mode in a few milliseconds. Thus, the responsiveness of thalamic circuits to the signals coming from the periphery may be under strict cortical control.

ACKNOWLEDGMENTS

Research supported by the Centre National de la Recherche Scientifique (CNRS), the Howard Hughes Medical Institute (HHMI) and the National Institutes of Health (NIH). All simulations were done using NEURON (Hines & Carnevale 1997). Supplementary information such as computer-generated movies are available on the Internet (http://cns.iaf.cnrs-gif.fr or http://www.cnl.salk.edu/∼alain/).

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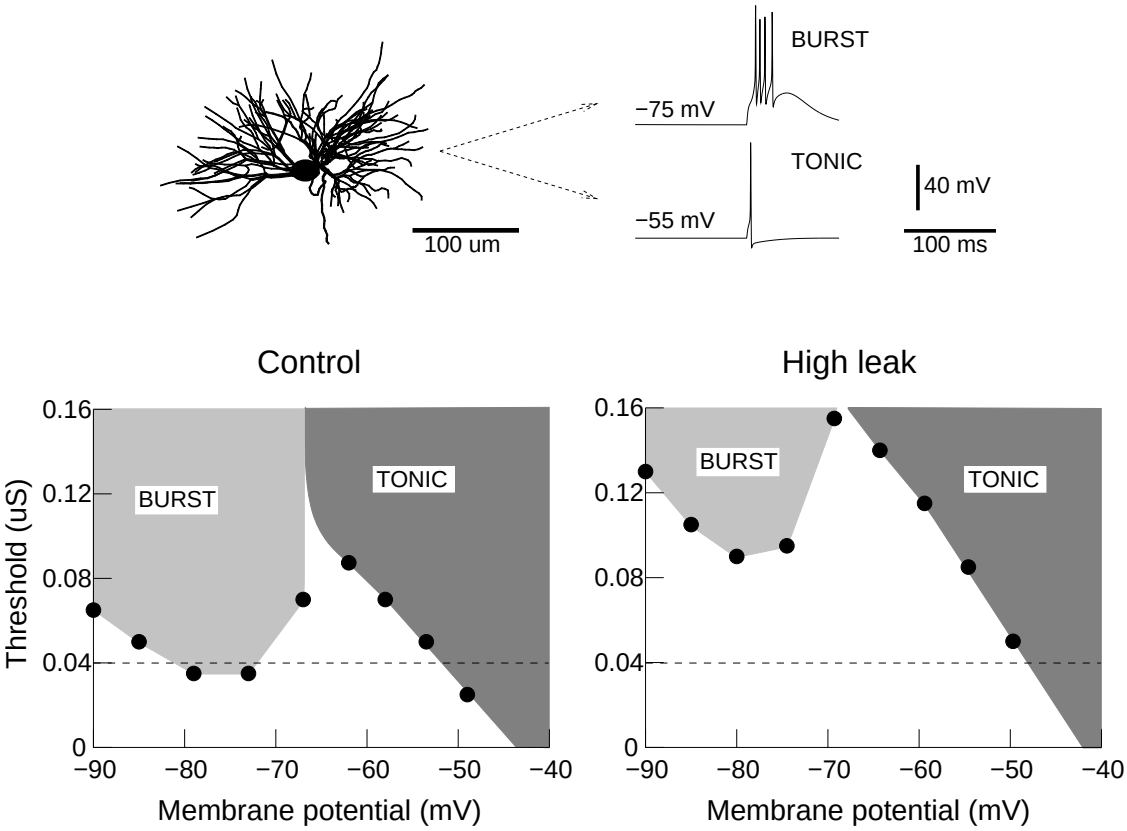

Figure 1:

Burst and tonic responses to excitatory synaptic currents in model thalamic relay neurons. *Top*: Thalamic relay neuron from rat ventrobasal nucleus, reconstructed and incorporated into simulations (Destexhe et al. 1998b). Examples of burst and tonic responses to excitatory (AMPA-mediated) synaptic stimuli are shown at two different voltages. *Bottom*: 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 Methods) 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 gray) and tonic modes (dark gray). *Control*: simulations using leak current estimated from whole-cell recordings *in vitro* (0.038 mS/cm^2). *High leak*: same simulations in the presence of a "leaky" membrane (leak conductance of 0.15 mS/cm^2), closer to *in vivo* conditions. The horizontal dotted 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.

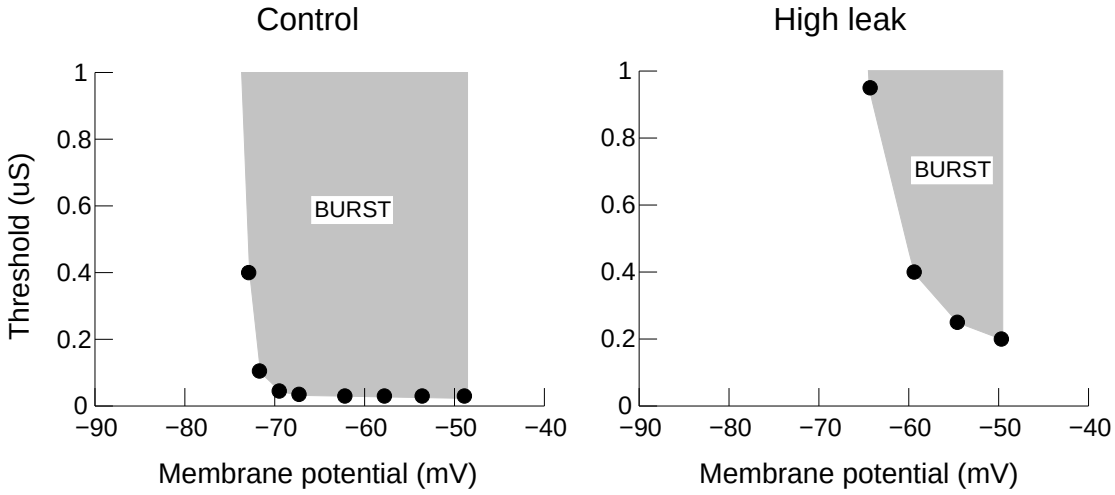

Figure 2:

Rebound burst responses of model thalamic relay neurons. The same model and paradigms as in Fig. 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. *Control*: burst responses obtained with leak conductances of 0.038 mS/cm^2. *High leak*: same simulations 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.

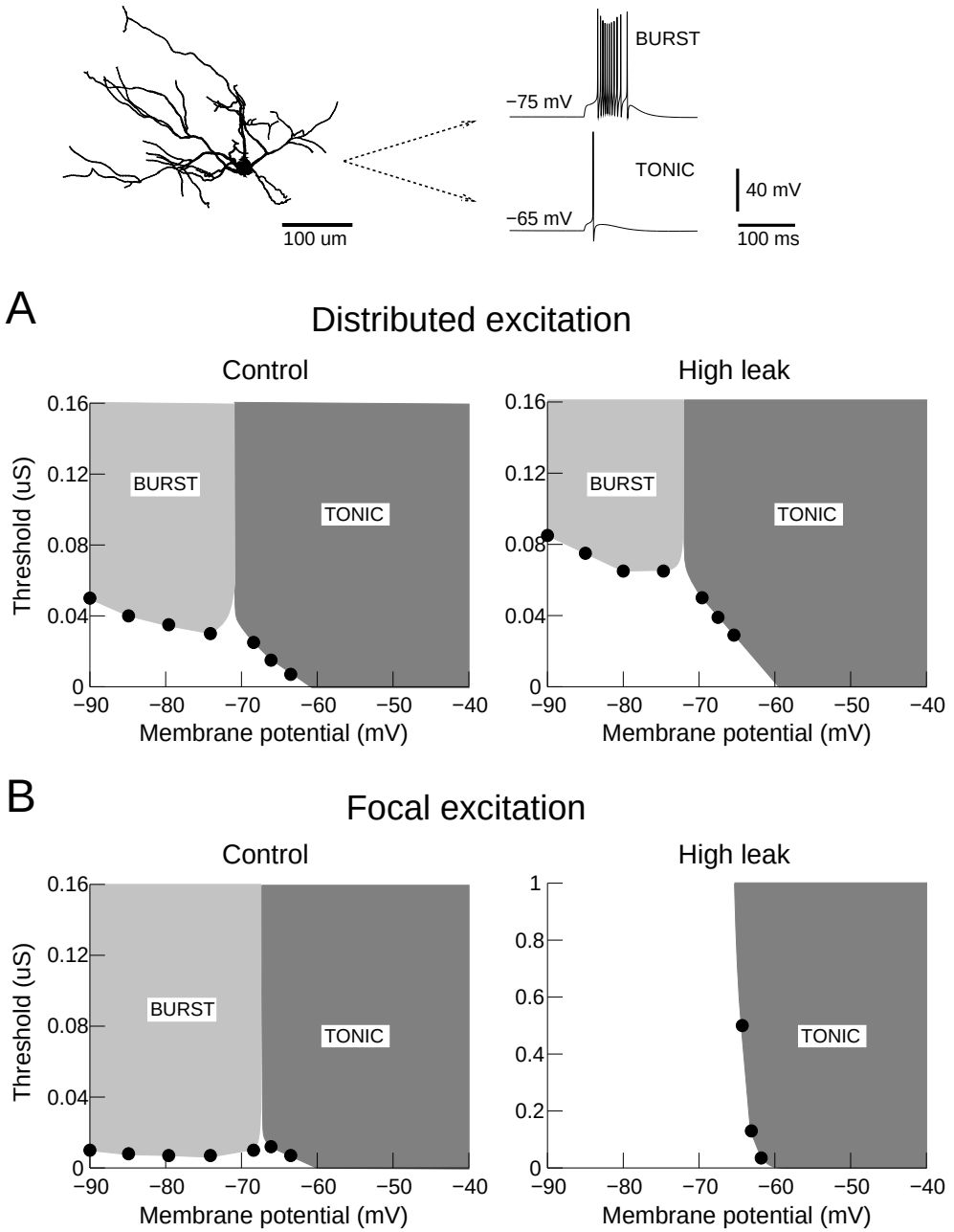

Figure 3:

Burst and tonic responses to excitatory synaptic currents in model thalamic reticular neurons. *Top*: Thalamic reticular neuron from rat ventrobasal 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. **A**. Responses obtained when excitatory conductances were distributed all through the dendrites with uniform conductance density. As in Fig. 1, burst and tonic responses are shown by gray regions (light gray for burst, and dark gray 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. **B.** Responses obtained when excitatory synapses were focally distributed in "hot spots" or in restricted regions of dendrites (in this case, distal dendrites at >250 μm from soma). The AMPA conductance density was always uniform in a given dendritic region). For both A and B, the responses are indicated for leak conductances estimated from whole-cell recordings (*Control*; g_{leak}=0.05 mS/cm^2), and for higher leak conductances (*High leak*; g_{leak}=0.15 mS/cm^2). The genesis of bursts was always more sensitive to EPSPs for focal inputs (B, *Control*), but was often very reduced or totally absent in a leaky membrane (B, *High leak*; note change of scale).

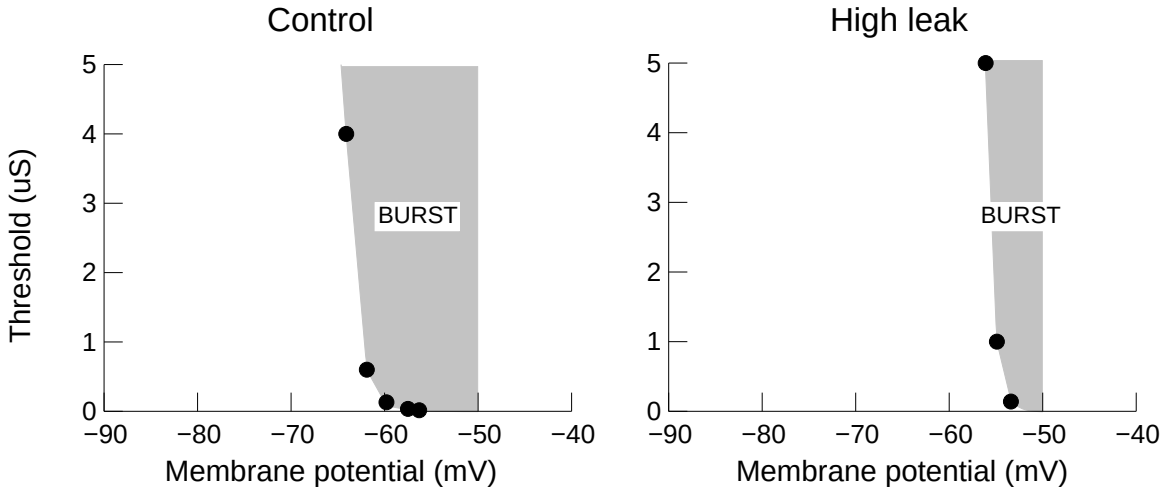

Figure 4:

Rebound burst responses in model thalamic reticular neurons. *Control*: Burst responses 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. *High leak*: 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. Compared to relay cells, the burst region was always smaller and larger IPSP conductances were generally needed to evoke rebound bursts (compare with Fig. 2).

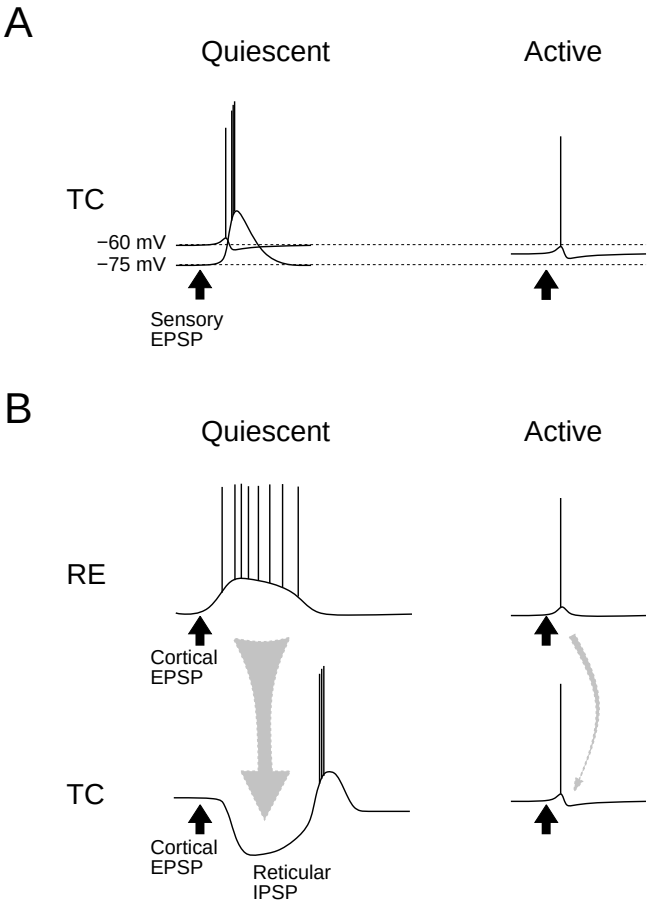

Figure 5:
Model predictions in terms of controlling the sensitivity of thalamic neurons. **A**. Responses to afferent (sensory) synapses. *Quiescent*: bursts can be evoked by sensory EPSPs in thalamocortical (TC) relay cells only at hyperpolarized membrane potentials and for sufficiently strong inputs. *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. *Quiescent*: the burst response of thalamic reticular (RE) neurons is sensitive to cortical EPSPs. These bursts generate a strong feedforward IPSP that dominates the cortical EPSP in TC cells. In this case, the cortex recruits relay cells through massive inhibition, and securely evoke an IPSP-rebound sequence in relay cells. *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 favoring the relay of information.