

# Thalamic and thalamocortical mechanisms underlying 3 Hz spike-and-wave discharges

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## Introduction

Paroxysmal ~3 Hz oscillations occur in thalamic and thalamocortical circuits during petit mal or absence epilepsy. Experiments in thalamic slices have revealed first, that thalamic circuits can generate oscillations at ~3 Hz following the application of antagonists of GABA<sub>A</sub> receptors and second, that the genesis of these oscillations is critically dependent on GABA<sub>B</sub>-mediated inhibition in thalamic relay neurons. The ionic mechanisms that are responsible for paroxysmal oscillations in thalamic slices can be explored in detailed models based on the known biophysical properties of thalamic neurons and the various types of synaptic currents that mediate interactions between them. These models, which provide a basic explanation for the frequency of the oscillations and the conditions that promote them, have been extended to include thalamocortical interactions. The recurrent excitation in the cortex and the corticothalamic feedback, together with GABA<sub>B</sub>-mediated inhibition in the thalamus, can account for many features of spike-and-wave oscillations, even when the thalamus is intact. These models generate detailed predictions that can be experimentally tested.

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Spike-and-wave epileptic seizures are characterized in humans by ~3 Hz oscillations in the electroencephalogram (EEG) (Fig. 1). These epileptic oscillations have a sudden onset, and the seizures invade the entire cerebral cortex simultaneously. Spike-and-wave patterns of similar characteristics are also seen in a number of experimental models in cats, rats, mice and monkeys.

The fact that EEG activity suddenly switches to spike-and-wave patterns (Fig. 1) suggests that it is generated in a central structure projecting widely to the cerebral cortex. The possible involvement of the thalamus in spike-and-wave seizures was initially suggested by Jasper and Kershman (1941) and is now supported by several findings. First, simultaneous thalamic and cortical recordings in humans during absence attacks demonstrated a clear thalamic participation during the seizures (Williams, 1953). The same study also showed that the oscillations usually started before signs of seizure appeared in the EEG. Second, a thalamic participation in human absence seizures was also shown by positron emission tomography (PET) (Pretvett et al., 1995). Third, electrophysiological recordings in experimental models of spike-and-wave seizures show that cortical and thalamic cells fire prolonged discharges in phase with the 'spike' component, while the 'wave' is characterized by a silence in all

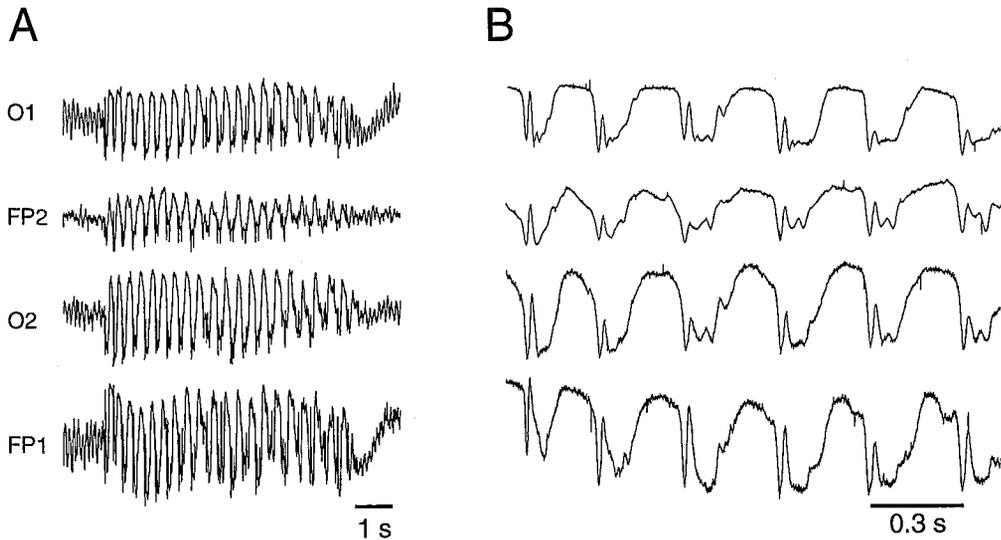


Fig. 1. Electroencephalogram (EEG) recording during a human absence seizure. A. The absence seizure lasted approximately five seconds and consisted of an oscillation at around 3 Hz which appeared nearly-simultaneously in all EEG leads. B. At higher temporal resolution, it is apparent that each cycle of the oscillation has interleaved spikes and waves. Channels FP1 and FP2 measured the potential differences between frontal and parietal regions of the scalp whereas channels O1 and O2 correspond to the measures between occipital regions. Modified from Destexhe, 1992.

cell types (Pollen, 1964; Steriade, 1974; Avoli et al., 1983; McLachlan et al., 1984; Buzsaki et al., 1988; Inoue et al., 1993; Seidenbecher et al., 1998). Electrophysiological recordings also indicate that spindle oscillations, which are generated by thalamic circuits (Steriade et al., 1990, 1993), can gradually be transformed into spike-and-wave discharges and all manipulations that promote or antagonize spindles have the same effect on spike-and-wave seizures (Kostopoulos et al., 1981a, 1981b; McLachlan et al., 1984). Finally, the spike-and-wave patterns disappear following thalamic lesions or by inactivating the thalamus (Pellegrini et al., 1979; Avoli and Gloor, 1981; Vergnes and Marescaux, 1992).

Although these results do suggest a thalamic origin for spike-and-wave seizures, there is also strong evidence that the cortex has a decisive role: thalamic injections of high doses of GABA<sub>A</sub> antagonists, such as penicillin (Ralston and Ajmone-Marsan, 1956; Gloor et al., 1977) or bicuculline (Steriade and Contreras, 1998) led to 3–4 Hz oscillations with no sign of spike-and-wave discharge. On the other hand, injection of the same drugs to the cortex, with no change in the thalamus,

resulted in seizure activity with spike-and-wave patterns (Gloor et al., 1977; Steriade and Contreras, 1998). The threshold for epileptogenesis was extremely low in the cortex compared to the thalamus (Steriade and Contreras, 1998). Finally, it was shown that a diffuse application of a dilute solution of penicillin to the cortex resulted in spike-and-wave seizures although the thalamus was intact (Gloor et al., 1977).

A series of pharmacological results suggest that  $\gamma$ -aminobutyric acid<sub>B</sub> (GABA<sub>B</sub>) receptors play a critical role in the genesis of spike-and-wave discharges. In rats, GABA<sub>B</sub> agonists exacerbate seizures, while GABA<sub>B</sub> antagonists suppress them (Hosford et al., 1992; Snead, 1992; Puigcerver et al., 1996; Smith and Fisher, 1996). More specifically, antagonizing thalamic GABA<sub>B</sub> receptors leads to the suppression of spike-and-wave discharges (Liu et al., 1992), which is another indication for a critical role of the thalamus.

There are inhibitory connections between neurons in the reticular nucleus of the thalamus (RE) and thalamocortical (TC) cells. The critical role for thalamic GABA<sub>B</sub> receptors on TC cells was established by investigating the action of clonaze-

pam, an anti-absence drug, in slices. Clonazepam diminishes GABA<sub>B</sub>-mediated inhibitory postsynaptic potentials (IPSPs) in TC cells, reducing their tendency to burst in synchrony (Huguenard and Prince, 1994a; Gibbs et al., 1996). The action of clonazepam appears to reinforce GABA<sub>A</sub> receptors in the RE nucleus (Huguenard and Prince, 1994a; Hosford et al., 1997). Indeed, there is a diminished frequency of seizures following reinforcement of GABA<sub>A</sub> receptors in the RE nucleus (Liu et al., 1991).

Perhaps the strongest evidence for the involvement of the thalamus was that in ferret thalamic

slices, spindle oscillations can be transformed into slower and more synchronized oscillations at ~3 Hz following blockade of GABA<sub>A</sub> receptors (Fig. 2; von Krosigk et al., 1993). This behavior is similar to the transformation of spindles to spike-and-wave discharges in cats following the systemic administration of penicillin, which acts as a weak GABA<sub>A</sub> receptor antagonist (Kostopoulos et al., 1981a, 1981b). Moreover, like spike-and-wave seizures in rats, the ~3 Hz paroxysmal oscillations in thalamic slices are suppressed by GABA<sub>B</sub> receptor antagonists (Fig. 2; von Krosigk et al., 1993).

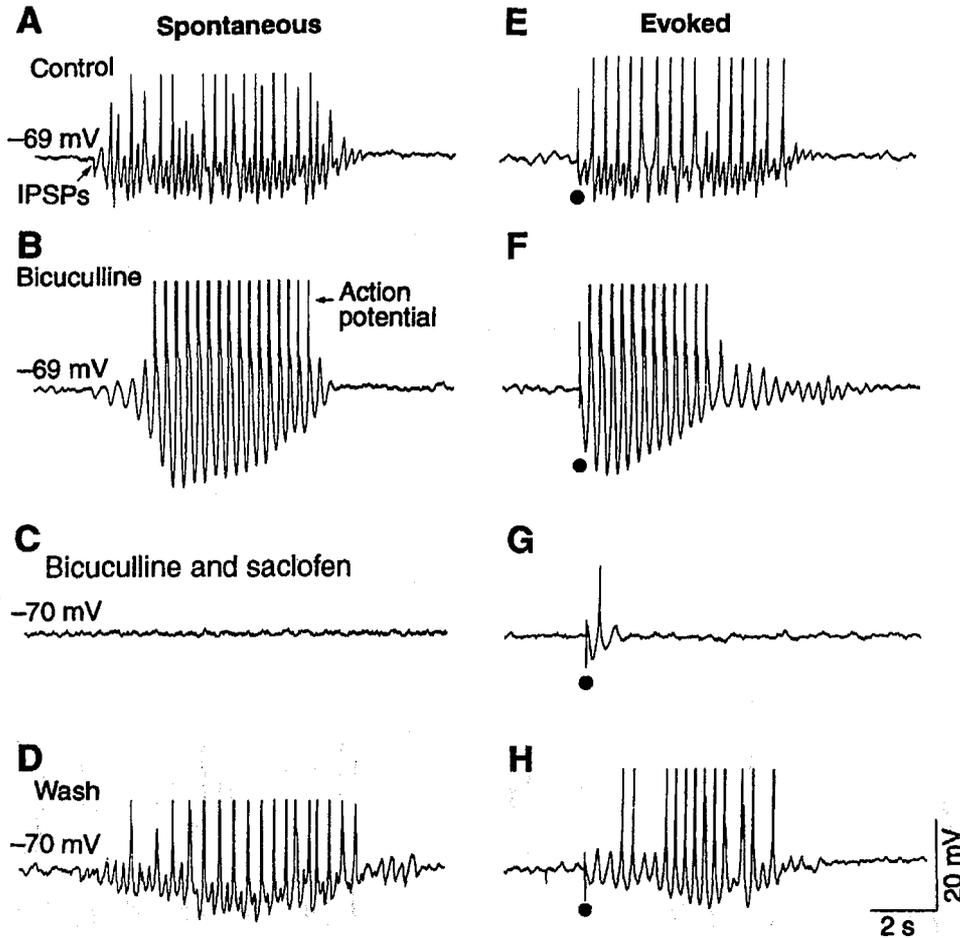


Fig. 2. Bicuculline-induced 3 Hz oscillation in thalamic slices. A. Control spindle sequence (~10 Hz) started spontaneously by an IPSP (arrow). B. Slow oscillation (~3 Hz) following block of GABA<sub>A</sub> receptors by bicuculline. C. Suppression of the slow oscillation in the presence of the GABA<sub>B</sub> antagonist baclofen. D. Recovery after wash. E-H indicate the same sequence as A-D but oscillations were triggered by stimulation of internal capsule. Modified from von Krosigk et al. (1993).

Taken together, these experiments suggest that both cortical and thalamic neurons are necessary to generate spike-and-wave rhythms, and that both GABA<sub>A</sub> and that GABA<sub>B</sub> receptors seem actively involved. However, the exact mechanisms are still unclear (Gloor and Fariello, 1988). In this paper, we review models for thalamic ~3 Hz paroxysmal oscillations and for thalamocortical ~3 Hz oscillations with spike-and-wave field potentials.

### Modeling the genesis of paroxysmal discharges in the thalamus

When the *in vitro* model of spindle waves was discovered (von Krosigk et al., 1993), it was also demonstrated that spindles can be transformed into ~3 Hz oscillations by blocking GABA<sub>A</sub> receptors (Fig. 2). It was further shown that this oscillation is sensitive to blockade of GABA<sub>B</sub> receptors by baclofen (Fig. 2) and is also suppressed by AMPA-receptor antagonists (von Krosigk et al., 1993). These *in vitro* experiments thus suggested that ~3 Hz paroxysmal thalamic oscillations are mediated by GABA<sub>B</sub> IPSPs (RE→TC) and AMPA EPSPs (TC→RE).

This possibility was investigated with computational models using a simple TC–RE circuit consisting of a single TC cell reciprocally connected to a single RE cell (scheme in Fig. 3; Destexhe et al., 1993b). The intrinsic firing behavior of the model TC cell was determined by  $I_T$  and  $I_h$ ; these currents were modeled using Hodgkin-Huxley (1952) type of models based on voltage-clamp data in TC cells. Calcium regulation of  $I_h$  was accounted for the waxing-and-waning of oscillations, as described previously (Destexhe et al., 1993a). The intrinsic firing properties of the RE cell were determined by  $I_T$ ,  $I_{K[Ca]}$  and  $I_{CAN}$  using Hodgkin-Huxley (1952) type kinetics and calcium-activated schemes as described previously (Destexhe et al., 1994a). The two cell types also included the fast  $I_{Na}$  and  $I_{Kd}$  currents necessary to generate action potentials with kinetics taken from Traub and Miles (1991). Synaptic interactions were mediated by glutamatergic and GABAergic receptors using kinetic models of postsynaptic receptors (Destexhe et al., 1994b, 1998b).

The two-neuron circuit displayed waxing-and-waning spindle oscillations at a frequency of

8–10 Hz (Fig. 3A; Destexhe et al., 1993b). The circuit also displayed a transformation to ~3 Hz oscillations when the kinetics of the GABAergic current were slow (Fig. 3; Destexhe et al., 1993b). The decay of inhibition greatly affected the frequency of the spindle oscillations, with slow decay corresponding to low frequencies. When the decay

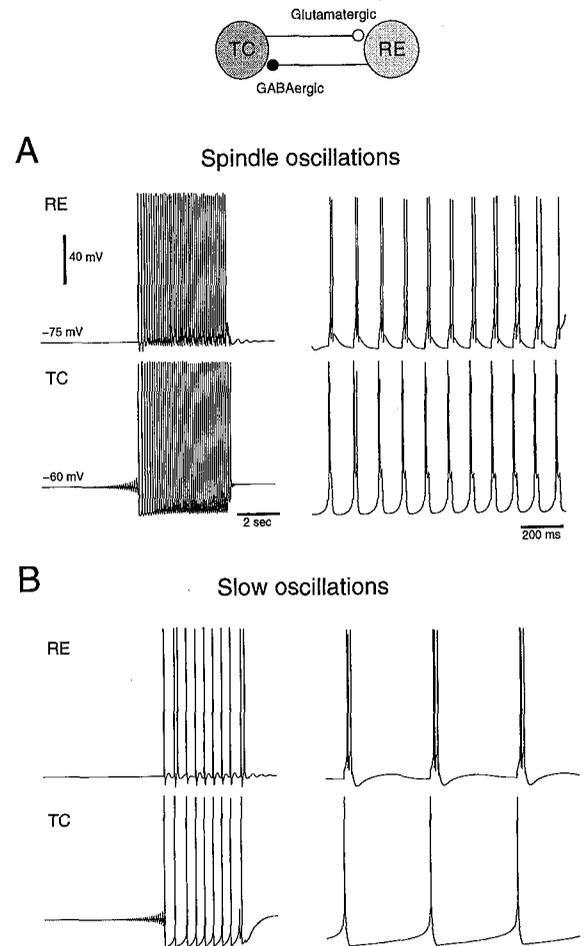


Fig. 3. Transition from 8–10 Hz spindle oscillations to ~3 Hz oscillations by slowing down the kinetics of GABAergic currents. A. 8–10 Hz spindle oscillations from a simple circuit consisting of one TC cell interconnected with one RE cell. The left panel shows a detail of a few cycles within the oscillation at 10 times higher resolution. Glutamatergic AMPA receptors were used from TC→RE and GABAergic GABA<sub>A</sub> receptors from RE→TC (decay rate constant  $\beta=0.1 \text{ ms}^{-1}$ ). B. Slower oscillations for slow GABAergic synapses. The decay rate constant of the GABAergic synapse was  $\beta=0.003 \text{ ms}^{-1}$ , similar to the decay rate of GABA<sub>B</sub> currents. Modified from Destexhe et al., 1993b.

was adjusted to match experimental recordings of GABA<sub>B</sub>-mediated currents (obtained from Otis et al., 1993), the circuit oscillated at around 3 Hz (Fig. 3B; Destexhe et al., 1993b).

Several mechanisms have been proposed to account for the effects of blocking of GABA<sub>A</sub> receptors in thalamic circuits (Wallenstein, 1994; Wang et al., 1995; Destexhe et al., 1996a; Golomb et al., 1996). The model of Wallenstein (1994) tested the proposition that disinhibition of interneurons projecting to TC cells with GABA<sub>B</sub> receptors may result in stronger discharges when GABA<sub>A</sub> receptors are antagonized (Soltesz and Crunelli, 1992). A model including TC, RE and interneurons (Wallenstein, 1994) reproduced the stronger discharges in TC cells following application of bicuculline. Although it is possible that this mechanism plays a role in thalamically-generated epileptic discharges, it does not account for experiments showing the decisive influence of the RE nucleus in preparations devoid of interneurons (Huguenard and Prince, 1994a, 1994b). Increased synchrony and stronger discharges were also reported in the model of Wang et al. (1995), but the synchronous state coexisted with a desynchronized state of the network, which has never been observed experimentally. The cooperative activation proposed for GABA<sub>B</sub> receptors (Destexhe and Sejnowski, 1995) produced robust synchronized oscillations and traveling waves at the network level (Golomb et al., 1996; Destexhe et al., 1996a), similar to those observed in thalamic slices (Kim et al., 1995). This property also led to the transformation of spindles to ~3 Hz paroxysmal oscillations following block of GABA<sub>A</sub> receptors (Destexhe et al., 1996a). These modeling studies reached the conclusion that the transition from spindle to paroxysmal patterns can be achieved provided there was cooperativity in GABA<sub>B</sub> responses. This is analyzed in more detail below.

#### *Models of the activation properties of GABA<sub>B</sub> responses*

Paroxysmal ~3 Hz discharges in the thalamus depend critically on GABA<sub>B</sub> responses. The underlying mechanisms have been explored with biophysical models (Destexhe and Sejnowski,

1995; Destexhe et al., 1996a). In these models, GABA<sub>B</sub> responses depended on the presynaptic pattern of activity and, in particular, GABA<sub>B</sub> inhibitory postsynaptic potentials (IPSPs) only occurred following long presynaptic bursts of spikes. This accounted for the different patterns of GABA<sub>B</sub> responses observed in the hippocampus (Dutar and Nicoll, 1988; Davies et al., 1990) and the thalamus (Huguenard and Prince, 1994b; Kim et al., 1997). This property is also important at the network level for the genesis of paroxysmal discharges in thalamic slices.

The biophysical model of GABA<sub>B</sub> responses included the release, diffusion and uptake of GABA, its binding on postsynaptic receptors and the activation of K<sup>+</sup> channels by G-proteins (Destexhe and Sejnowski, 1995). The model tested the possibility that postsynaptic mechanisms could explain the non-linear stimulus dependence observed for GABA<sub>B</sub> responses. A model incorporating extracellular diffusion of GABA was necessary to account for features of GABA<sub>B</sub> responses in the hippocampus, where GABA spillover may be significant due to the high density of GABAergic terminals. In contrast, no spillover was necessary to explain thalamic GABAergic responses, which is consistent with the sparse aggregates of inhibitory terminals on TC cell dendrites (Liu et al., 1995b). Simulating the properties of GABA<sub>B</sub> responses in the thalamus therefore required a source of non-linearity located in the postsynaptic response rather than GABA spillover (Destexhe and Sejnowski, 1995). We hypothesized that this non-linearity arose from the transduction mechanisms underlying the activation of K<sup>+</sup> channels by G-proteins. The assumption that 4 G-proteins must bind to K<sup>+</sup> channels to open them provided the nonlinearity required to account for GABA<sub>B</sub> responses (Destexhe and Sejnowski, 1995); this is consistent with the tetrameric structure of K<sup>+</sup> channels (Hille, 1992).

The properties of GABAergic responses in thalamic slices were simulated using models of RE cells based on the presence of a low-threshold calcium current and lateral GABA<sub>A</sub>-mediated synaptic interactions within the RE nucleus (Fig. 4A; Destexhe and Sejnowski, 1995). Under normal conditions, stimulation in the RE nucleus evoked

biphasic IPSPs in TC cells, with a rather small GABA<sub>B</sub> component (Fig. 4B). We mimicked an increase of intensity by increasing the number of RE cells discharging. The ratio between GABA<sub>A</sub> and GABA<sub>B</sub> IPSPs was independent of the intensity of stimulation in the model (Destexhe and Sejnowski, 1995), as observed experimentally (Huguenard and Prince, 1994b). However, this ratio could be changed by blocking GABA<sub>A</sub> receptors locally in the RE nucleus, leading to enhanced burst discharge in RE cells and a more prominent GABA<sub>B</sub>

component in TC cells (Fig. 4C). This is consistent with the effect of clonazepam in reinforcing the GABA<sub>A</sub> IPSPs in the RE nucleus, resulting in diminished GABA<sub>B</sub> IPSPs in TC cells (Huguenard and Prince, 1994a).

These simulations suggest that, because of the characteristic properties of GABA<sub>B</sub> receptors, the output of the RE nucleus onto TC cells is determined by the presence of GABA<sub>A</sub> interactions between RE cells. The presence of these GABA<sub>A</sub> synapses restricts the bursts of RE cells to few spikes and leads to IPSPs dominated by GABA<sub>A</sub> in TC cells. However, when this lateral inhibition is suppressed, RE cells produced prolonged bursts and evoked IPSPs dominated by GABA<sub>B</sub> in TC cells. Such a relationship between GABA<sub>B</sub> receptor activation and presynaptic discharge has been observed experimentally in dual intracellular recordings (Kim et al., 1997; Thomson and Destexhe, 1999). The consequences of this mechanism for generating ~3 Hz oscillations in thalamic circuits are analyzed below.

#### *Genesis of ~3 Hz oscillations in thalamic circuits*

To explain the genesis of ~3 Hz paroxysmal oscillations in thalamic circuits, we investigated first the effect of GABA<sub>A</sub> vs. GABA<sub>B</sub> stimulation of TC cells. The thalamic circuit model was identical to that in a previous study (Destexhe et al., 1996a). TC cells had  $I_T$ ,  $I_h$ ,  $I_{Na}$  and  $I_{Kd}$  currents, and RE cells had  $I_{T3}$ ,  $I_{Na}$  and  $I_{Kd}$  currents which were modeled using Hodgkin-Huxley kinetics based on voltage-clamp data. Calcium-dependent upregulation of  $I_h$  was included on TC cells to account for the waxing-and-waning of spindle oscillations. Synaptic interactions were modeled by AMPA receptors (TC → RE) and a mixture of GABA<sub>A</sub> and GABA<sub>B</sub> receptors (RE → TC), with GABA<sub>B</sub> modeled as described above. Details of the model can be found in Destexhe et al. (1996a).

Mimicking the output of the thalamic reticular network in Fig. 4B–C, a model TC cell was stimulated with presynaptic bursts of action potentials acting on GABA<sub>A</sub> and GABA<sub>B</sub> receptors (Fig. 5). For brief bursts (3 spikes at 360 Hz), mimicking the output of the RE nucleus in control conditions (Fig. 4B), the TC cell produced subharmonic bursting similar to spindle oscillations (Fig. 5A).

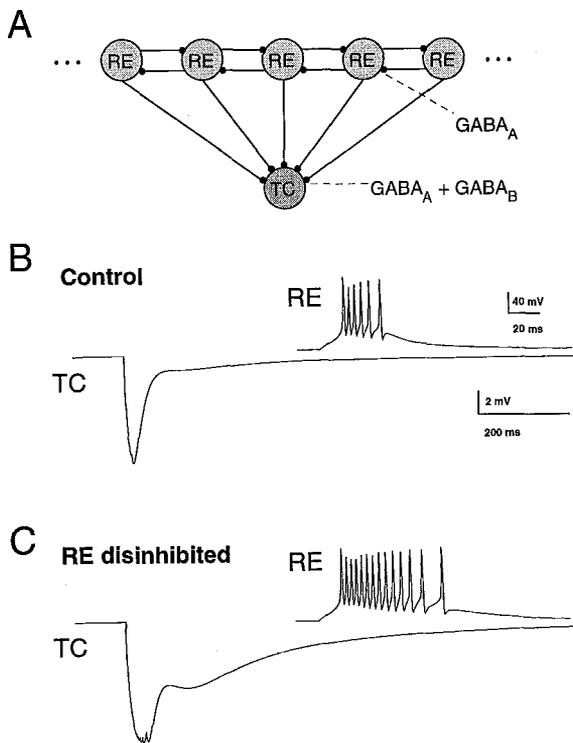


Fig. 4. Simulation of the effect of lateral inhibition in the thalamic reticular nucleus. GABA<sub>B</sub> response were enhanced in thalamocortical cells through disinhibition in the thalamic reticular nucleus. A. Connectivity: a simple network of RE cells was simulated with GABA<sub>A</sub> receptor-mediated synaptic interactions. All RE cells project to a single TC cell with synapses containing both GABA<sub>A</sub> and GABA<sub>B</sub> receptors. Models of the RE cells were taken from Destexhe et al. (1994a). B. In control conditions, the bursts generated in RE cells by stimulation have 2–8 spikes (inset) and evoke in TC cells a GABA<sub>A</sub>-dominated IPSP with a small GABA<sub>B</sub> component. C. When GABA<sub>A</sub> receptors are suppressed in RE, the bursts become much larger (inset) and evoke in TC cells a stronger GABA<sub>B</sub> component. Modified from Destexhe and Sejnowski, 1995.

The suppression of GABA<sub>A</sub> conductances in model RE cells produced prolonged discharges, as described above. When such prolonged discharges were used as the presynaptic signal (7 spikes at 360 Hz), mimicking the output of the disinhibited RE nucleus (Fig. 4C), strong GABA<sub>B</sub> IPSPs were activated and the TC cell could follow a stimulation at 3.3 Hz (Fig. 5B). The TC-cell bursts were larger due to the more complete deinactivation of I<sub>T</sub> provided by GABA<sub>B</sub> IPSPs.

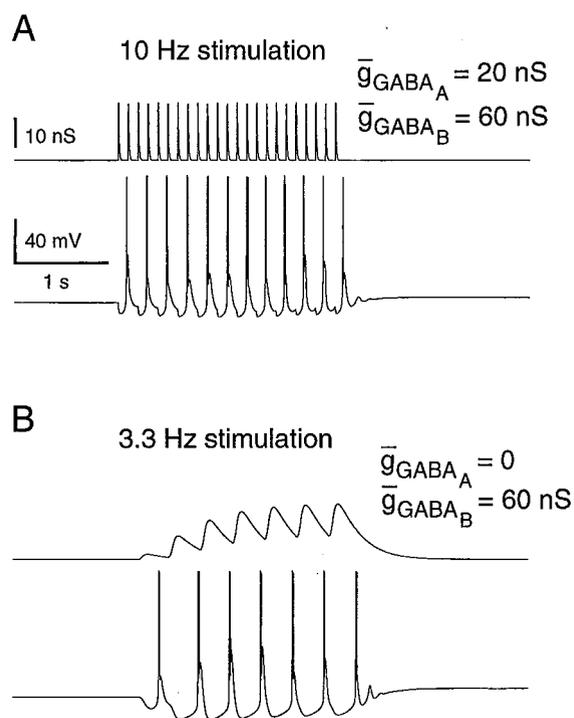


Fig. 5. Simulated responses of thalamocortical cells to 10 Hz or 3 Hz stimulation on GABA<sub>A</sub> and GABA<sub>B</sub> receptors. A. 10 Hz stimulation with trains of 3 pulses at 360 Hz, occurring every 100 ms. The GABA<sub>A</sub> conductance is represented (top trace) with the membrane potential (bottom). B. 3.3 Hz stimulation of GABA<sub>B</sub> receptors alone (the GABA<sub>B</sub> conductance is drawn on top). In this case, seven successive bursts were simulated with an interburst period of 300 ms; each burst in the stimulus consisted of a train of 18 pulses at 360 Hz. In contrast to the stimuli in A which evoked a weak GABA<sub>B</sub> component in the IPSP (see Fig. 4, the stimulus used in B evoked strong GABA<sub>B</sub>-mediated currents and the TC cell was recruited in secure rebound bursts responses. These TC bursts were larger due to the more complete deinactivation of I<sub>T</sub> provided by GABA<sub>B</sub> IPSPs. Modified from Destexhe et al., 1996a.

The properties analyzed above (Figs. 4–5) can explain the experimental observation that blockade of GABA<sub>A</sub> receptors by application of bicuculline transform the spindle behavior into a slower (3–4 Hz) highly synchronous oscillation that are dependent on GABA<sub>B</sub> receptors (von Krosigk et al., 1993; Bal et al., 1995; Kim et al., 1995). These properties were integrated in models of thalamic circuits (Fig. 6A; Destexhe et al., 1996a). In control conditions (Fig. 6B), the circuit generated spindle oscillations. Suppression of GABA<sub>A</sub> receptors led to slower oscillations (Fig. 6C). These oscillations were a consequence of the properties of GABA<sub>B</sub> responses as described in Fig. 4. Following removal of GABA<sub>A</sub>-mediated inhibition, the RE cells could produce prolonged bursts that evoked strong GABA<sub>B</sub> currents in TC cells. These prolonged IPSPs evoked robust rebound bursts in TC cells (as in Fig. 5B), and TC bursts in turn elicited bursting in RE cells through EPSPs. This mutual TC-RE interactions recruited the system into a 3–4 Hz oscillation, with characteristics similar to those of bicuculline-induced paroxysmal oscillations in ferret thalamic slices. The mechanisms responsible for these oscillations were similar to those that give rise to normal spindle oscillations, but the shift in the balance of inhibition leads to oscillations that were slower and more synchronized (see details in Destexhe et al., 1996a).

### Model of spike-and-wave oscillations in the thalamocortical system

Experiments reviewed in the Introduction show that the thalamus is essential to generate 3 Hz spike-and-wave seizures, and indeed thalamic slices display paroxysmal oscillations at ~3 Hz following application of GABA<sub>A</sub> antagonists, as analyzed in detail above. However, evidence from a number of experimental studies indicate that this thalamic 3 Hz oscillation is a phenomenon distinct from spike-and-wave seizures. Injections of GABA<sub>A</sub> antagonists in the thalamus with intact cortex failed to generate spike-and-wave seizures (Ralston and Ajmone-Marsan, 1956; Gloor et al., 1977; Steriade and Contreras, 1998). In these *in vivo* experiments, suppressing thalamic GABA<sub>A</sub> receptors led to 'slow spindles' around 4 Hz, quite different from

spike-and-wave oscillations. On the other hand, spike-and-wave discharges were obtained experimentally by diffuse application of GABA<sub>A</sub>

antagonists to the cortex (Gloor et al., 1977). Therefore, *in vivo* experiments indicate that spindles transform into spike-and-wave discharges by

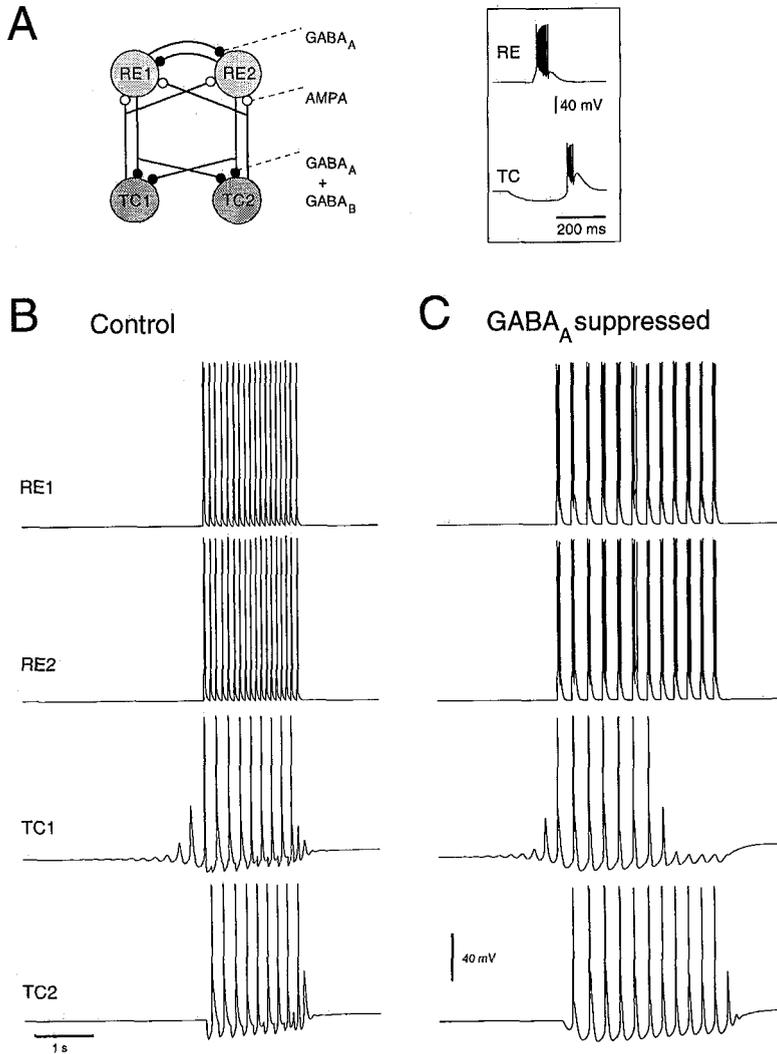


Fig. 6. Oscillations in a four-neuron circuit of thalamocortical and thalamic reticular cells. A. Left: circuit diagram consisting of two TC and two RE cells. Synaptic currents were mediated by AMPA/kainate receptors (from TC to RE;  $\bar{g}_{AMPA} = 0.2 \mu S$ ), a mixture of GABA<sub>A</sub> and GABA<sub>B</sub> receptors (from RE to TC;  $\bar{g}_{GABA_A} = 0.02 \mu S$  and  $\bar{g}_{GABA_B} = 0.04 \mu S$ ) and GABA<sub>A</sub>-mediated lateral inhibition between RE cells ( $\bar{g}_{GABA_A} = 0.2 \mu S$ ). Right: inset showing the simulated burst responses of TC and RE cells following current injection (pulse of 0.3 nA during 10 ms for RE and -0.1 nA during 200 ms for TC). B. Spindle oscillations arose as the first TC cell (TC1) started to oscillate, recruiting the two RE cells, which in turn recruited the second TC cell. The oscillation was maintained for a few cycles and repeated with silent periods of 15–25 s. C. Slow 3–4 Hz oscillation obtained when GABA<sub>A</sub> receptors were suppressed, mimicking the effect of bicuculline. The first TC cell (TC1) started to oscillate, recruiting the two RE cells, which in turn recruited the second TC cell. The mechanism of recruitment between cells was identical to spindle oscillations, but the oscillations were more synchronized, of slower frequency, and had a 15% longer silent period. The burst discharges were prolonged due to the loss of lateral inhibition in the RE. Modified from Destexhe et al., 1996a.

altering cortical inhibition without changes in the thalamus. We therefore investigated a thalamocortical model to explore possible mechanisms to explain these observations and to relate them to the 3 Hz thalamic oscillation (Destexhe, 1998).

*Intact thalamic circuits can be forced into ~3 Hz oscillations due to GABA<sub>B</sub> receptors*

The first question we address is how the behavior of thalamic circuits is controlled by the cortex. Thalamic networks have a propensity to generate oscillations on their own, such as the 7–14 Hz spindle oscillations (Steriade et al., 1993; von Krosigk et al., 1993). Although these oscillations are generated in the thalamus, the neocortex can trigger them (Steriade et al., 1972; Roy et al., 1984; Contreras and Steriade, 1996) and corticothalamic feedback exerts a decisive control over thalamic oscillations (Contreras et al., 1996).

In computational models, this cortical control required more powerful corticothalamic EPSPs on RE cells compared to TC cells (Destexhe et al., 1998a). In these conditions, excitation of corticothalamic cells led to mixed EPSPs and IPSPs in TC cells, in which the IPSP was dominant, consistent with experimental observations (Burke and Sefton, 1966; Deschênes and Hu, 1990). If cortical EPSPs and IPSPs from RE cells were of comparable conductance, cortical feedback could not evoke oscillations in the thalamic circuit due to shunting effects between EPSPs and IPSPs (Destexhe et al., 1998a). The most likely reason for the experimental and modeling evidence for ‘inhibitory dominance’ in TC cells is that RE cells are extremely sensitive to cortical EPSPs (Contreras et al., 1993), probably due to powerful T-current in their dendrites (Destexhe et al., 1996b). In addition, cortical synapses contact only the distal dendrites of TC cells (Liu et al., 1995a) and are probably attenuated for this reason. Taken together, these data suggest that corticothalamic feedback operates mainly by eliciting bursts in RE cells, which in turn evoke powerful IPSPs on TC cells that largely overwhelm the direct cortical EPSPs.

The effects of corticothalamic feedback on the thalamic circuit was investigated with the thalamic model (Fig. 7; Destexhe, 1998). Simulated cortical

EPSPs evoked bursts in RE cells (Fig. 7B, arrow), which recruited TC cells through IPSPs, and triggered a ~10 Hz oscillation in the circuit. During the oscillation, TC cells rebound once every 2 cycles following GABA<sub>A</sub>-mediated IPSPs and RE cells only discharged a few spikes, evoking GABA<sub>A</sub>-mediated IPSPs in TC cells with no significant GABA<sub>B</sub> currents (Fig. 7B). These features are typical of spindle oscillations (Steriade et al., 1993; von Krosigk et al., 1993).

However, a different type of oscillatory behavior could be elicited from the circuit by repetitive stimulation at 3 Hz with high intensity (14 spikes every 333 ms; Fig. 7C). All cell types were entrained to discharge in synchrony at ~3 Hz. On the other hand, repetitive stimulation at 3 Hz at low intensity produced spindle oscillations (Fig. 7D) similar to Fig. 7A. High-intensity stimulation at 10 Hz led to quiescence in TC cells (Fig. 7E), due to sustained GABA<sub>B</sub> currents, similar to a previous analysis (see Fig. 12 in Lytton et al., 1997).

These simulations indicate that strong corticothalamic feedback at 3 Hz can force thalamic circuits in a 3 Hz oscillation (Destexhe, 1998). Cortical EPSPs force RE cells to fire large bursts (Fig. 7C, arrows), fulfilling the conditions needed to activate GABA<sub>B</sub> responses. The consequence was that TC cells were ‘clamped’ at hyperpolarized levels by GABA<sub>B</sub> IPSPs during ~300 ms before they could rebound. The non-linear properties of GABA<sub>B</sub> responses are therefore responsible here for the coexistence between two types of oscillations in the same circuit: moderate corticothalamic feedback recruited the circuit in ~10 Hz spindle oscillations, while strong feedback at 3 Hz could force the intact circuit at the same frequency due to the nonlinear activation properties of intrathalamic GABA<sub>B</sub> responses.

*~3 Hz spike-and-wave oscillations in thalamocortical circuits*

A thalamocortical network consisting of different layers of cortical and thalamic cells was simulated to explore the impact of this mechanism at the network level (Destexhe, 1998). The network included thalamic TC and RE cells, and a simplified representation of the deep layers of the cortex, in which pyramidal (PY) cells constitute the major

source of corticothalamic fibers. As corticothalamic PY cells receive a significant proportion of their excitatory synapses from ascending thalamic axons (Hersch and White, 1981; White and Hersch, 1982), these cells mediate a monosynaptic excitatory feedback loop (thalamus-cortex-thalamus)

which was modeled here. The structure of the network, with TC, RE, PY and cortical interneurons (IN), is schematized in Fig. 8A. Each cell type contained the minimal set of calcium- and voltage-dependent currents necessary to account for their intrinsic properties: TC cells contained  $I_T$ ,

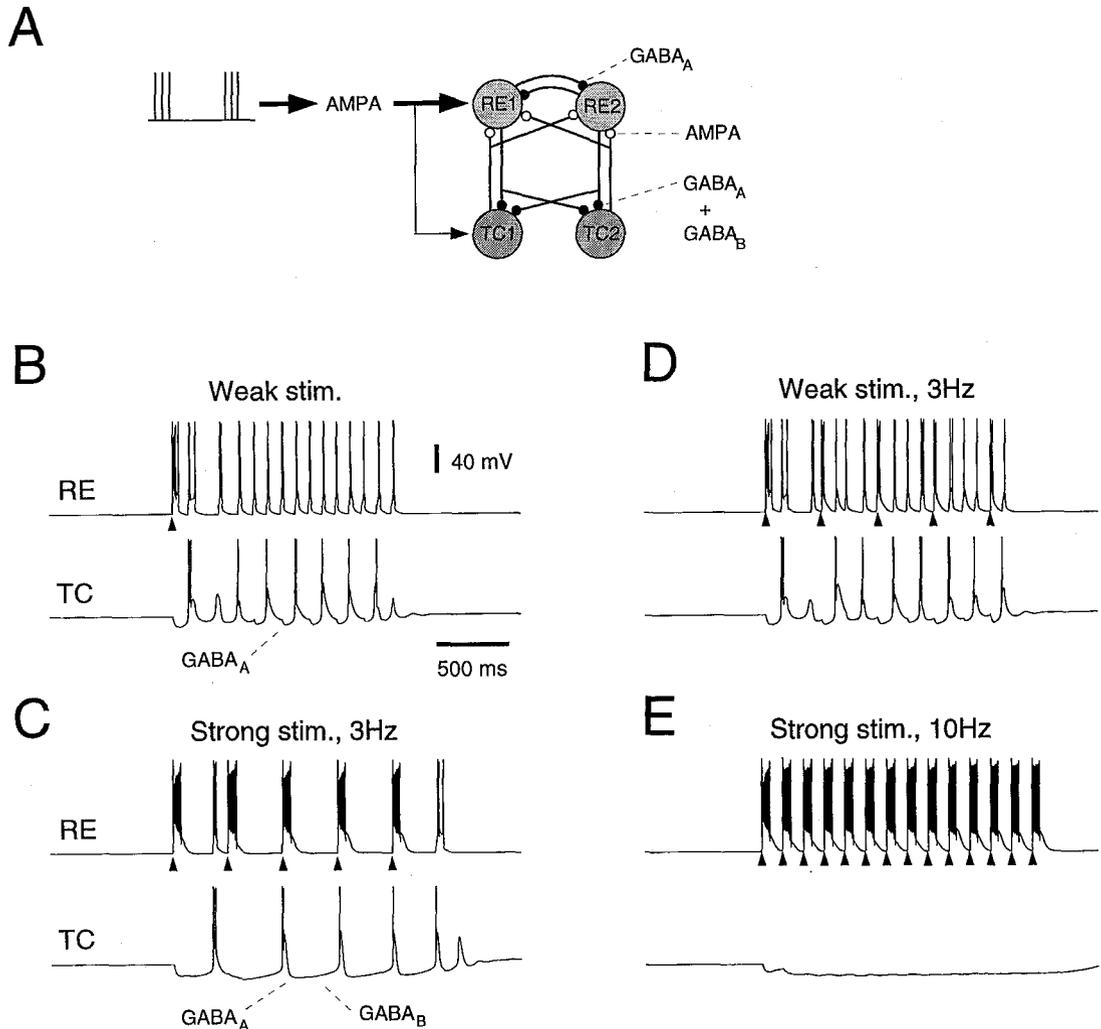


Fig. 7. Corticothalamic feedback can force thalamic circuits into  $\sim 3$  Hz oscillations due to the properties of GABA<sub>B</sub> receptors. A. Connectivity and receptor types in a circuit of thalamocortical (TC) and thalamic reticular (RE) neurons. Corticothalamic feedback was simulated through AMPA-mediated synaptic inputs (shown on the left of the connectivity diagram; total conductance of  $1.2 \mu\text{S}$  to RE cells and  $0.01 \mu\text{S}$  to TC cells). B. A single stimulation of corticothalamic feedback (arrow) entrained the circuit into a 10 Hz mode similar to spindle oscillations. C. With a strong-intensity stimulation at 3 Hz (arrows; 14 spikes/stimulus), RE cells were recruited into large bursts, which evoked IPSPs onto TC cells dominated by GABA<sub>B</sub>-mediated inhibition. In this case, the circuit could be entrained into a different oscillatory mode, with all cells firing in synchrony. D. Weak stimulation at 3 Hz (arrows) entrained the circuit into spindle oscillations (identical intensity as in B). E. Strong stimulation at 10 Hz (arrows) led to quiescent TC cells due to sustained GABA<sub>B</sub> current (identical intensity as in C). Modified from Destexhe, 1998.

$I_h$  and a calcium-dependent upregulation of  $I_h$ , RE cells contained  $I_{TS}$ , PY cells had a slow voltage-dependent  $K^+$  current  $I_M$  responsible for

spike-frequency adaptation similar to 'regular-spiking' pyramidal cells (Connors and Gutnick, 1990). All cell types had the  $I_{Na}$  and  $I_{Kd}$  currents

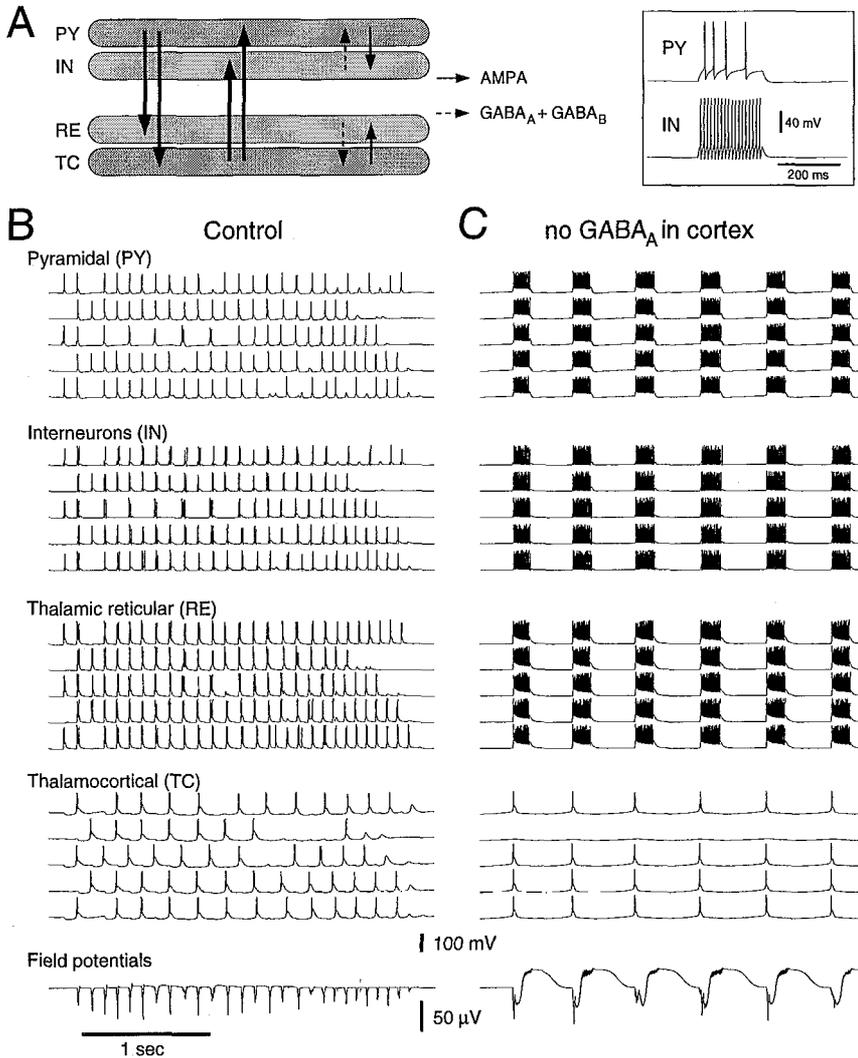


Fig. 8. Transformation of spindle oscillations into  $\sim 3$  Hz spike-and-wave oscillations by reducing cortical inhibition. A. Connectivity between different cell types: 100 cells of each type were simulated, including TC and RE cells, cortical pyramidal cells (PY) and interneurons (IN). The connectivity is shown by continuous arrows, representing AMPA-mediated excitation, and dashed arrows, representing mixed GABA<sub>A</sub> and GABA<sub>B</sub> inhibition. In addition, PY cells were interconnected using AMPA receptors and RE cells were interconnected using GABA<sub>A</sub> receptors. The inset shows the repetitive firing properties of PY and IN cells following depolarizing current injection (0.75 nA during 200 ms;  $-70$  mV rest). B. Spindle oscillations in the thalamocortical network in control conditions. 5 cells of each type, equally spaced in the network, are shown (0.5 ms time resolution). The field potentials, consisting of successive negative deflections at  $\sim 10$  Hz, is shown at the bottom. C. Oscillations following the suppression of GABA<sub>A</sub>-mediated inhibition in cortical cells with thalamic inhibition intact. All cells displayed prolonged discharges in phase, separated by long periods of silences, at a frequency of  $\sim 2$  Hz. GABA<sub>B</sub> currents were maximally activated in TC and PY cells during the periods of silence. Field potentials (bottom) displayed spike-and-wave complexes. Thalamic inhibition was intact in B and C. Modified from Destexhe, 1998.

necessary to generate action potentials. All currents were modeled using Hodgkin–Huxley (1952) type kinetics based on voltage-clamp data. Synaptic interactions were mediated by glutamate AMPA and NMDA receptors, as well as GABAergic GABA<sub>A</sub> and GABA<sub>B</sub> receptors, and were simulated using kinetic models of postsynaptic receptors (Destexhe et al., 1994b, 1998b). All excitatory connections (TC→RE, TC→IN, TC→PY, PY→PY, PY→IN, PY→RE, PY→TC) were mediated by AMPA receptors, some inhibitory connections (RE→TC, IN→PY) were mediated by a mixture of GABA<sub>A</sub> and GABA<sub>B</sub> receptors, while intra-RE connections were mediated by GABA<sub>A</sub> receptors. Simulations were also performed using NMDA receptors added to all excitatory connections (with maximal conductance set to 25% of the AMPA conductance) and no appreciable difference was observed. They were not included in the present model. Extracellular field potentials were calculated from postsynaptic currents in PY cells according to the model of Nunez (1981) and assuming that all cells were arranged equidistantly in a one dimensional layer (see details in Destexhe, 1998).

In control conditions (Fig. 8B), the thalamocortical network generated synchronized spindle oscillations with cellular discharges in phase between in all cell types, as observed experimentally (Contreras and Steriade, 1996). TC cells discharged on average once every two cycles following GABA<sub>A</sub>-mediated IPSPs, while all other cell types discharged roughly at every cycle at ~10 Hz, consistent with the typical features of spindle oscillations observed intracellularly (Steriade et al., 1990; von Krosigk et al., 1993). The simulated field potentials displayed successive negative deflections at ~10 Hz (Fig. 8B), in agreement with the pattern of field potentials during spindle oscillations (Steriade et al., 1990). This pattern of field potentials was generated by the limited discharge in PY cells, which fired roughly one spike per oscillation cycle.

Diffuse application of the GABA<sub>A</sub> antagonist penicillin to the cortex, with no change in thalamus, leads to spike-and-wave oscillations in cats (Gloor et al., 1977). In the model, this situation was simulated by decreasing GABA<sub>A</sub> conductances in

cortical cells, with thalamus left intact. Alteration of GABA<sub>A</sub> receptors in the cortex had a considerable impact in generating spike-and-wave. Under these conditions, the spindle oscillations transformed into 2–3 Hz oscillations (Fig. 8C; Destexhe, 1998). The field potentials generated by these oscillations reflected a pattern of spikes and waves (Fig. 8C, bottom).

Spike-and-wave discharges developed progressively from spindle oscillations. Reducing the intracortical fast inhibition from 100% to 50% increased the occurrences of prolonged high-frequency discharges during spindle oscillations (Destexhe, 1998). Further decrease in intracortical fast inhibition led to fully-developed spike-and-wave patterns similar to Fig. 8C (Destexhe, 1998). Field potentials displayed one or several negative/positive sharp deflections, followed by a slowly-developing positive wave (Fig. 8C, bottom). During the ‘spike’, all cells fired prolonged high-frequency discharges in synchrony, while the ‘wave’ was coincident with neuronal silence in all cell types. This portrait is typical of experimental recordings of cortical and thalamic cells during spike-and-wave patterns (Pollen, 1964; Steriade 1974; Avoli et al., 1983; McLachlan et al., 1984; Buzsaki et al., 1988; Inoue et al., 1993; Seidenbecher et al., 1998). Some TC cells stayed hyperpolarized during the entire oscillation (second TC cell in Fig. 8C), as also observed experimentally (Steriade and Contreras, 1995). A similar oscillation arose if GABA<sub>A</sub> receptors were suppressed in the entire network (not shown).

These simulations suggest that spindles can be transformed into an oscillation with field potentials displaying spike-and-wave, and that this transformation can occur by alteration of cortical inhibition with no change in the thalamus, in agreement with spike-and-wave discharges obtained experimentally by diffuse application of diluted penicillin onto the cortex (Gloor et al., 1977). The mechanism of the ~3 Hz oscillation of this model depends on a thalamocortical loop where both cortex and thalamus are necessary, but none of them generates the 3 Hz rhythmicity alone (see details in Destexhe, 1998).

Removing intrathalamic GABA<sub>A</sub>-mediated inhibition also affected the oscillation frequency,

but did not generate spike-and-wave, because pyramidal cells were still under the strict control of cortical fast inhibition (Destexhe, 1998). This is in agreement with *in vivo* injections of bicuculline into the thalamus, which exhibited slow oscillations with increased thalamic synchrony, but no spike-and-wave patterns in the field potentials (Ralston and Ajmone-Marsan, 1956; Steriade and Contreras, 1998).

In the model, spike-and-wave oscillations may follow a similar waxing-and-waning envelope as spindles, and were a network consequence of the properties of a single ion channel ( $I_h$ ) in TC cells (Destexhe, 1998). A calcium-dependent upregulation of  $I_h$  was included in TC cells similar to previous models (Destexhe et al., 1993a, 1996a). The possibility that  $I_h$  upregulation underlies the waxing-and-waning of spindles at the level of thalamic networks has been demonstrated *in vitro* (Bal and McCormick, 1996; Luthi and McCormick, 1998) and predicted by models (Destexhe et al., 1993b; 1996a). This mechanism may also underlie the waxing-and-waning of spindles at the level of thalamocortical networks (Destexhe et al., 1998a). The present model suggests that the upregulation of  $I_h$  in TC cells is responsible for temporal modulation of spike-and-wave oscillations and may evoke several cycles of spike-and-wave oscillations, interleaved with long periods of silence ( $\sim 20$  sec), as is observed experimentally in sleep spindles and spike-and-wave epilepsy, thus emphasizing further the resemblance between the two types of oscillation.

#### *A thalamocortical loop mechanism for $\sim 3$ Hz spike-and-wave oscillations*

During spindles, the oscillation is generated by intrathalamic interactions (TC-RE loops) and is reinforced by thalamocortical loops, as suggested in a previous model (Destexhe et al., 1998a). The combined action of intrathalamic and thalamocortical loops provides RE cells with moderate excitation, which evokes GABA<sub>A</sub>-mediated IPSPs in TC cells and sets the frequency to  $\sim 10$  Hz. During spike-and-wave oscillations, an increased cortical excitability provides corticothalamic feedback that is strong enough to force prolonged burst

discharges in RE cells, which in turn evokes IPSPs in TC cells dominated by the GABA<sub>B</sub> component. In this case, the prolonged inhibition sets the frequency to  $\sim 3$  Hz and the oscillation is generated by a thalamocortical loop in which the thalamus is intact (see details in Destexhe, 1998). Therefore, if the cortex is inactivated during spike-and-wave, this model predicts that the thalamus should resume generating spindle oscillations, as observed experimentally in cats treated with penicillin (Gloor et al., 1979).

Figure 9 shows the phase relations between the different cell types in this model of spike-and-wave. High-frequency discharges generated 'spike' components in the field potentials, whereas 'wave' components were generated by GABA<sub>B</sub> IPSPs in PY cells due to the prolonged firing of cortical interneurons. The hyperpolarization of PY cells during the 'wave' also contained a significant contribution from the voltage-dependent K<sup>+</sup> current  $I_M$ , which was maximally activated due to the prolonged discharge of PY cells during the 'spike'. The 'wave' component in this model is therefore due to two types of K<sup>+</sup> currents, one intrinsic and the other GABA<sub>B</sub>-mediated. The relative contribution of each current to the 'wave' depends on their respective conductance values (see details in Destexhe, 1998).

The 'spike' component was generated by a concerted prolonged discharge of all cell types. However, the discharges were not perfectly in phase, as indicated in Fig. 9B. There was a significant phase advance of TC cells, as observed experimentally (Inoue et al., 1993; Seidenbecher et al., 1998). This phase advance was responsible for the initial negative spike in the field potentials, which coincided with the first spike in the TC cells (Fig. 9B, dashed line). This feature implements the precedence of EPSPs over IPSPs in the PY cell in order to generate spike-and-wave complexes. The simulations therefore suggest that the initial spike of spike-and-wave complex is due to thalamic EPSPs that precede other synaptic events in PY cells (Destexhe, 1998). Thalamic EPSPs may also trigger an initial avalanche of discharges due to pyramidal cell firing, before IPSPs arises, which would also result in a pronounced negative spike component in field potentials.

## Discussion

This paper reviewed experiments and models that provide a new view for the genesis of spike-and-wave oscillations in thalamocortical systems. The proposed mechanism for spike-and-wave discharges is summarized here and corroborating experimental evidence and predictions are presented.

### *A mechanism for spike-and-wave*

The primary biophysical component of this mechanism is the activation properties of GABA<sub>B</sub>

receptors. In the model of GABA<sub>B</sub> receptor activation based on a G-protein kinetic scheme, a multiplicity of G-protein binding sites accounted for the nonlinearities of GABA<sub>B</sub> responses (Destexhe and Sejnowski, 1995). At the level of thalamic networks, this property is responsible for the coexistence of two types of oscillations: spindle oscillations for moderate discharges, insufficient to activate GABA<sub>B</sub> responses, and slow paroxysmal oscillations for prolonged discharge patterns, for which GABA<sub>B</sub> responses are maximal (Fig. 6C; Destexhe et al., 1996a). These properties can account for the slow paroxysmal oscillations observed in thalamic slices following block of

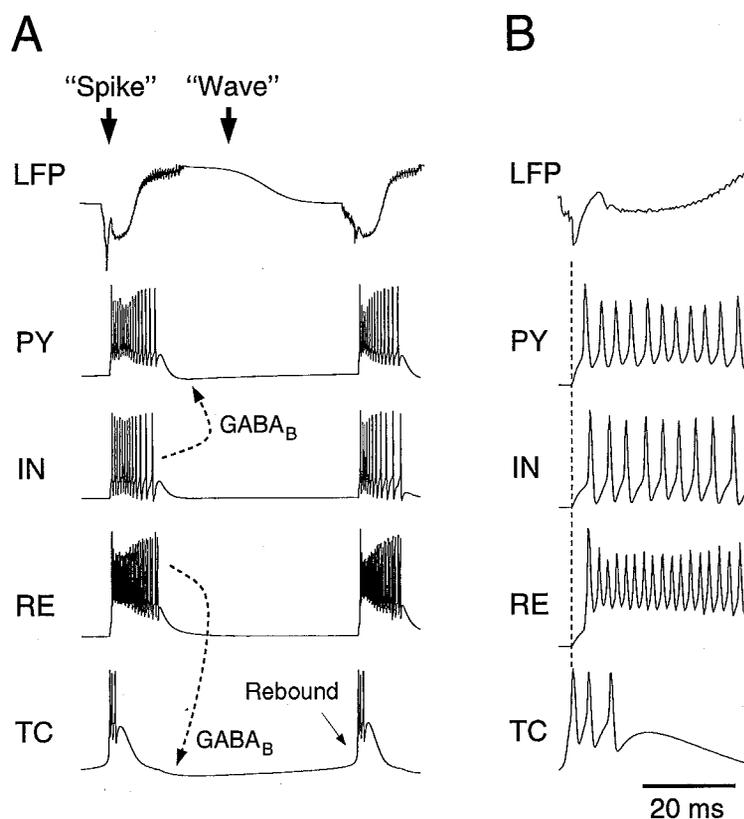


Fig. 9. Phase relationships during simulated spike-and-wave discharges. A. Local field potentials (LFP) and representative cells of each type during spike-and-wave oscillations. *Spike*: all cells displayed prolonged discharges in synchrony, leading to spiky field potentials. *Wave*: the prolonged discharge of RE and IN neurons evoked maximal GABA<sub>B</sub>-mediated IPSPs in TC and PY cells respectively (dashed arrows), stopping the firing of all neuron types during a period of 300–500 ms, and generating a slow positive wave in the field potentials. The next cycle restarted due to the rebound of TC cells following GABA<sub>B</sub> IPSPs (arrow). B. Phase relationships in the thalamocortical model. TC cells discharged first, followed by PY, RE and IN cells. The initial negative peak in the field potentials coincided with the first spike in TC cells before PY cells started firing, and was generated by thalamic EPSPs in PY cells. Modified from Destexhe, 1998.

GABA<sub>A</sub> receptors (Fig. 2: von Krosigk et al., 1993) and fully agree with dual intracellular recordings in ferret thalamic slices (Kim et al., 1997).

A second component of this mechanism is the powerful corticothalamic feedback. We propose that corticothalamic feedback operates mainly on RE cells, resulting in a dominant IPSP in TC cells. This mechanism can account for the properties of spindle oscillations (Destexhe et al., 1998a). With this type of corticothalamic feedback, cortical EPSPs can force *intact* thalamic circuits to fire at the same frequency as the slow paroxysmal oscillation (Fig. 7C; Destexhe, 1998). If cortical EPSPs are strong enough, RE cells are forced into prolonged burst discharges and evoke GABA<sub>B</sub> IPSPs in TC cells. This mechanism could be tested experimentally, which provides an important prediction of this model (see details in Destexhe, 1998).

A third component is the strong corticothalamic feedback provided by an increased excitability in cortical networks. If GABA<sub>A</sub> inhibition is reduced in cortex, pyramidal cells generate exceedingly strong discharges, which are strong enough to entrain the thalamus in the 3 Hz mode. At the network level, reducing cortical GABA<sub>A</sub> receptor function leads to ~3 Hz oscillations with all cell types generating prolonged discharge patterns. Simulated field potentials indicate that this pattern of firing generates spike-and-wave waveforms (Fig. 8C; Destexhe, 1998).

#### *Similarities and differences with experimental data*

This model is consistent with a number of experimental results on spike-and-wave epilepsy: (a) thalamic and cortical neurons discharge in synchrony during the 'spike' while the 'wave' is characterized by neuronal silence (Pollen, 1964; Steriade 1974; Avoli et al., 1983; McLachlan et al., 1984; Buzsaki et al., 1988; Inoue et al., 1993; Seidenbecher et al., 1998), similar to Fig. 9A; (b) TC cells firing precedes that of other cell types, followed by cortical cells and RE cells (Inoue et al., 1993; Seidenbecher et al., 1998), similar to the phase relations in the present model (Fig. 9B); (c) spike-and-wave patterns disappear following either removal of the cortex (Avoli and Gloor, 1982) or

the thalamus (Pellegrini et al., 1979; Vergnes and Marescaux, 1992), as predicted by the present mechanism; (d) antagonizing thalamic GABA<sub>B</sub> receptors suppresses spike-and-wave discharges (Liu et al., 1992), consistent with this model; and (e) spindle oscillations can be gradually transformed into spike-and-wave discharges (Kostopoulos et al., 1981a, 1981b), as observed in this model (Destexhe, 1998).

This model also emphasizes a critical role for the RE nucleus. Reinforcing GABA<sub>A</sub>-mediated inhibition in the RE nucleus will antagonize the genesis of large burst discharges in RE cells by corticothalamic EPSPs, antagonizing the genesis of GABA<sub>B</sub>-mediated IPSPs in TC cells, therefore suppresses spike-and-wave discharges (Destexhe, 1998). This property is consistent with the diminished frequency of seizures observed following reinforcement of GABA<sub>A</sub> receptors in the RE nucleus (Liu et al., 1991) and the suppression of spike-and-wave following chemical lesion of the RE nucleus (Buzsaki et al., 1988). It is also consistent with the action of the anti-absence drug clonazepam, which acts by preferentially enhancing GABA<sub>A</sub> responses in the RE nucleus (Hosford et al., 1997), leading to diminished GABA<sub>B</sub>-mediated IPSPs in TC cells (Huguenard and Prince, 1994a; Gibbs et al., 1996). In addition, reinforcing the T-current in RE cells lowered the threshold for spike-and-wave in the model (Destexhe, 1998), consistent with experimental observations (Tsakiridou et al., 1995).

The model is also consistent with the failure to observe spike-and-wave from injections of GABA<sub>A</sub> antagonists in the thalamus (Ralston and Ajmone-Marsan, 1956; Gloor et al., 1977; Steriade and Contreras, 1998). In the model, suppressing thalamic GABA<sub>A</sub> receptors led to 'slow spindles' around 4 Hz, distinctly different from spike-and-wave oscillations (Destexhe, 1998). In this case, the discharge of pyramidal cells was controlled by cortical GABA<sub>A</sub>-mediated inhibition and, due to this strict control, no prolonged discharges and no spike-and-wave patterns were generated in the cortex.

On the other hand, a number of experimental observations are not consistent with the present model. First, an apparent intact cortical inhibition

was reported in cats treated with penicillin (Kostopoulos et al., 1983). However, this study did not distinguish between GABA<sub>A</sub> and GABA<sub>B</sub>-mediated inhibition. In the present model, even when GABA<sub>A</sub> was antagonized, IPSPs remained of approximately the same size because cortical interneurons fired stronger discharges (Fig. 8C) and led to stronger GABA<sub>B</sub> currents. There was a compensation effect between GABA<sub>A</sub> and GABA<sub>B</sub>-mediated IPSPs (not shown), which may lead to the misleading observation that inhibition is preserved.

Second, some GABA<sub>A</sub> agonists, like barbiturates, may increase the frequency of seizures (Vergnes et al., 1984), possibly through interactions with GABA<sub>A</sub> receptors in TC cells (Hosford et al., 1997). A similar effect was seen in the model (Destexhe, 1998), but this effect was weak. More accurate simulation of these data would require modeling the variants of GABA<sub>A</sub> receptor types in different cells to address how the threshold for spike-and-wave discharges is affected by various types of GABAergic conductances. These points will be considered in future models.

Third, the present model only investigated a thalamocortical loop scenario for the genesis of spike-and-wave oscillations but other mechanisms could also contribute. Although most experimental data favor a mechanism involving both the thalamus and the cortex (see Introduction), a number of experimental studies also point to a possible intracortical mechanism for spike-and-wave. Experiments revealed spike-and-wave in isolated cortex or athalamic preparations in cats (Marcus and Watson, 1966; Pellegrini et al., 1979; Steriade and Contreras, 1998). However, this type of paroxysmal oscillation had a different morphology from the typical 'thalamocortical' spike-and-wave pattern and was also slower in frequency (1–2.5 Hz vs. 3.5–5 Hz; Pellegrini et al., 1979). By contrast, intracortical spike-and-wave discharges were not observed in athalamic rats (Vergnes and Marescaux, 1992). Since no intracellular recordings were made during the presumed spike-and-wave discharges in the cat isolated cortex, it is not clear if this oscillation represents the same spike-and-wave paroxysm as in the intact thalamocortical system. Future models should investigate the

possibility of intracortically-generated spike-and-wave when more precise experimental data will be available.

In conclusion, the models summarized here provide insights into a thalamocortical loop mechanism that may be responsible for spike-and-wave discharges based on the intrinsic and synaptic properties of thalamic and cortical cells. The qualitative characteristics displayed by the simulations are consistent with several experimental models of spike-and-wave, as well as with thalamic slice experiments. A critical element of the model is the high sensitivity of RE cells to cortical EPSPs. Since thalamic RE cells may generate bursts of spikes through dendritic T-currents (Destexhe et al., 1996b), strategies to suppress seizures could be developed that focus on these dendrites.

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