ELSEVIER

Neurocomputing 38–40 (2001) 529–538

NEUROCOMPUTING

www.elsevier.com/locate/neucom

Corticothalamic feedback can induce hypersynchronous low-frequency rhythms in the physiologically intact thalamus

Damien Debay[a], Alain Destexhe[a,b], Thierry Bal[a,*]

[a]*Unité de Neurosciences Intégratives et Computationnelles, CNRS, UPR-2191, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France*

[b]*Département de Physiologie, Université Laval, Pavillon F. Vandry, Québec G1K 7P4, Canada*

Abstract

Thalamic circuits are capable of generating oscillations of different frequency and level of synchrony. However, it is not known how these oscillation types are controlled in the intact brain. Here we consider the influence of corticothalamic feedback onto the thalamus by using thalamic slices and computational models. Models predicted that strong activation of corticothalamic feedback should transform the normal spindle oscillations (6–10 Hz) into hypersynchronous slow (2–4 Hz) oscillations. By implementing this feedback paradigm in ferret thalamic slices, we could observe this transformation. Thalamic reticular neurons show a dramatic increase of firing, but not interneurons, suggesting that this effect is mediated mostly through the reticular nucleus. We conclude that cortical inputs can induce slow hypersynchronous oscillations in the physiologically intact thalamus, which has clear implications for understanding the genesis of pathologies such as absence seizures, and more generally the downstream control of thalamic nuclei by the cerebral cortex.

Keywords: Thalamus; Cortex; Absence epilepsy; Seizures

1. Introduction

Thalamic circuits can display different types of oscillations, corresponding to various frequencies and level of synchrony. The most common rhythmical activity exhibited by intact thalamic circuits is the 6–14 Hz spindle rhythm, which consists of

* Corresponding author.
E-mail address: bal@iaf.cnrs-gif.fr (D. Debay).

0925-2312/01/$ - see front matter
PII: S0925-2312(01)00398-8

waxing and waning oscillations recurring periodically [5,21,24]. Blockade of $GABA_A$ receptors by application of bicuculline turns this rhythm into a slower and more synchronized oscillation [2,3,24]. The frequency of this oscillation (2–4 Hz) is strikingly similar to the typical 3 Hz frequency of absence seizures in humans, for which the thalamus is thought to be a key player [15]. The thalamus also displays fast oscillations in the gamma frequency range (20–60 Hz) in vivo, which may play a role in visual processing [20].

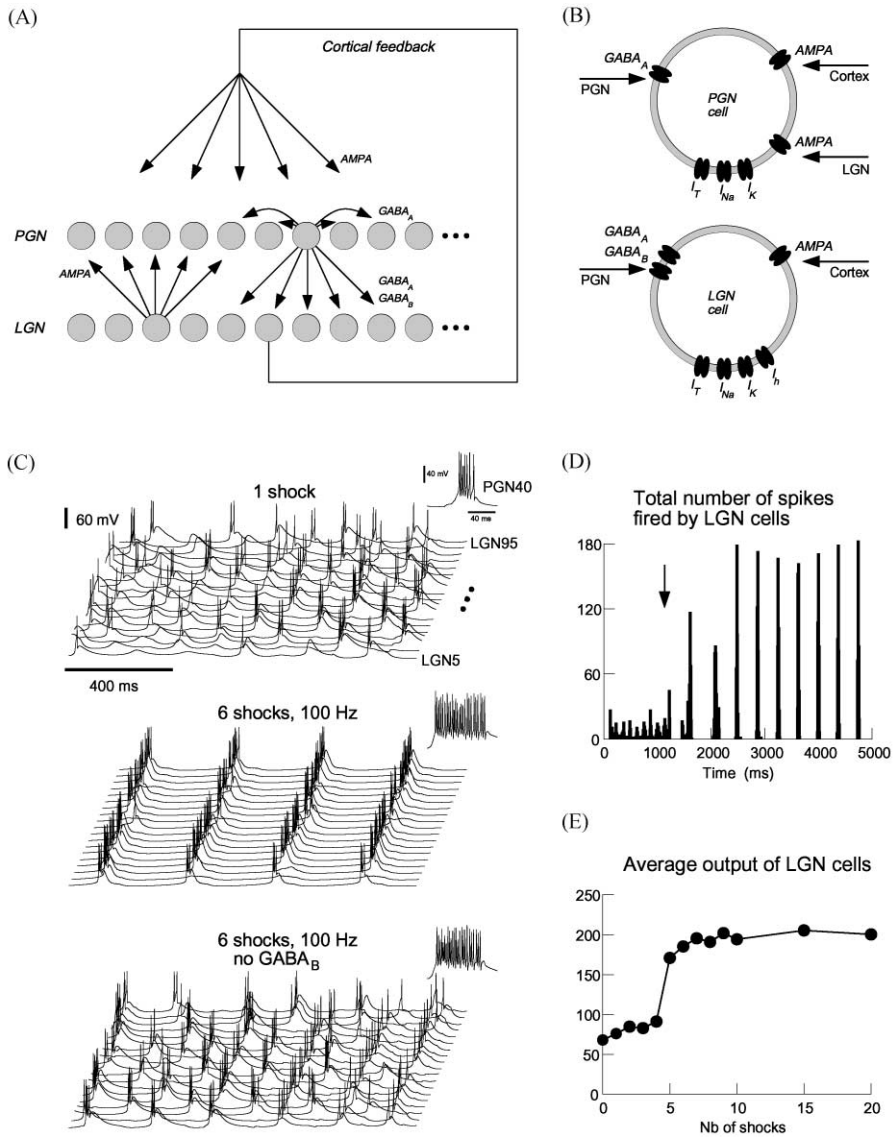
While corticothalamic synapses are considerably dense in the thalamus [13,14,18,19], little is known about their role in oscillatory genesis. It has been shown that corticothalamic feedback is essential in synchronizing different thalamic nuclei into large-scale coherent oscillations [5] or synchronizing individual thalamic neurons into fast oscillations [20]. Corticothalamic feedback could also have the ability to control the type of oscillation displayed by thalamic circuits, which is the main prediction formulated by a model of absence seizures [8]. We test here this prediction by performing stimulation of corticothalamic feedback fibers in vitro, combined with computational models.

2. Methods

Intracellular and extracellular recordings were performed in slices of adult ferrets (3–15 months old) at a temperature of 34.5–35.5°C. Thalamic slices contained interconnected lateral geniculate (LGN) and perigeniculate (PGN) layers. All experimental procedures were detailed previously [1–3,24]. Electrical stimulation of the corticothalamic fibers (optic radiation, OR) was performed using bipolar tungsten electrodes. Feedback stimulations of corticothalamic fibers was triggered by the activity of thalamic relay cells using a home-made data acquisition software (Acquis1; developed by G. Sadoc, CNRS Gif-sur-Yvette, ANVAR et Biologic), which allows the setting of a voltage threshold for detection of relay cell discharges in intracellular and multiunit recordings and a latency after which a command is sent to a stimulating unit (A360; WPI).

Fig. 1. Models predict that corticothalamic feedback can control thalamic oscillations in the intact thalamus. (A) Scheme of the feedback paradigm. A thalamic network consisting of two one-dimensional layers of LGN and PGN neurons (100 cells each) was simulated with topographic connections mediated by glutamate (AMPA) receptors and GABAergic ($GABA_A$ and $GABA_B$ receptors) as indicated. One cell (LGN cell $\#10$) was the trigger of the cortical feedback, which was simulated through AMPA conductances in all cell types. (B) Scheme of the different ionic mechanisms present in each cell type. (C) Simulation of the feedback experiment. Top: Feedback stimuli consisting of a single shock produced bursting patterns typical of spindle oscillations. Middle: Strong feedback (6 shocks at 100 Hz) synchronized the burst discharges of LGN cells and switched the oscillation frequency to 3 Hz in the entire network, although only one cell served as the trigger. Bottom: The removal of $GABA_B$ receptors suppressed the ability of the feedback to induce the 3 Hz rhythm. Each graph represents 19 equally spaced LGN cells in the network and an example of PGN burst is shown in inset. A delay of 25 ms was used in the feedback loop. (D) Histogram of the number of spikes fired by the LGN population. The arrow indicates the onset of the feedback (6 shocks, 100 Hz). (E) Average number of spikes fired by the LGN population at each cycle of the oscillation, represented against the number of shocks. Figure modified from Ref. [1].

Computational models of thalamic neurons were designed based on previous studies [10,11]. LGN and PGN neurons were modeled by single compartment representations including various intrinsic voltage- and calcium-dependent currents, such as I_T, I_h, I_{Na}, I_K in LGN cells and I_T, I_{Na}, I_K in PGN. These intrinsic currents were represented by Hodgkin–Huxley type models. In addition, I_h contained an upregulation by intracellular calcium as described previously [10]. LGN and PGN neurons generated bursts of action potentials with a strength and voltage-dependence similar to experiments.



Postsynaptic currents mediated by glutamate (AMPA and NMDA receptors) and GABA ($GABA_A$ and $GABA_B$ receptors) were simulated using kinetic models of postsynaptic receptors [12]. The interaction LGN → PGN was mediated by AMPA receptors, while the PGN → LGN interaction involved a mixture of $GABA_A$ and $GABA_B$ receptors (Fig. 1(A) and (B)), as found experimentally [24]. Corticothalamic feedback was mediated by AMPA receptors on both LGN and PGN cells. NMDA receptors were also used in some simulations (not shown; conductance of 25% of that of AMPA receptors), which did not affect the present results.

Feedback simulations were designed similar to the experiments reported here. In a network consisting of two one-dimensional layers of 100 LGN and 100 PGN cells, a single LGN cell was chosen as trigger (Fig. 1(A)). When this LGN cell fired, the first spike was used to trigger a burst of stimulation of corticothalamic feedback receptors, after a delay of 10–50 ms. As in experiments, the number and strength of stimuli were varied.

3. Results

We investigated the hypothesis that corticothalamic feedback can control the type of oscillation displayed by the thalamus. We first show this paradigm in the model, then investigate it in slices of the ferret lateral geniculate nucleus (LGN). We finally return to the model to evaluate how the control of thalamic oscillations will impact on the cortex.

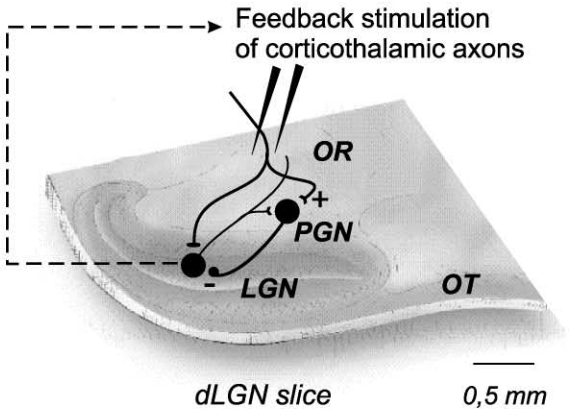
3.1. Computational models predict that thalamic oscillations can be controlled by cortical feedback

The feedback paradigm consisted of forming an artificial feedback loop between the activity of the LGN neurons and the stimulation of corticothalamic fibers (Figs. 1(A)). We first investigated this paradigm in biophysically based models of thalamic circuits. A network of 100 PGN and 100 LGN cells interconnected via AMPA, $GABA_A$ and $GABA_B$ receptors was simulated (Fig. 1(A)). Cellular models were single-compartments incorporating calcium- and voltage-dependent currents (Fig. 1(B)) needed to reproduce the burst discharges of thalamic neurons [10].

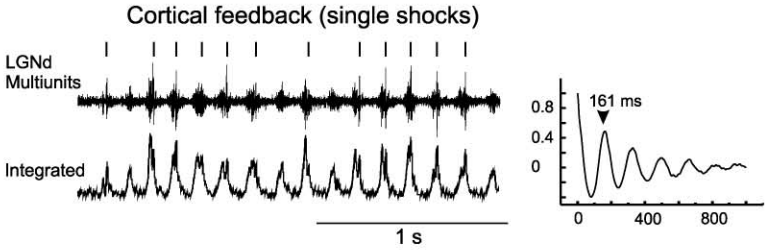
Similar to the prediction formulated earlier [8], the strength of the feedback had a decisive impact on the type of oscillation displayed by the circuit (Fig. 1(C)): feedback consisting of 1–4 shocks at 100 Hz led to patterns of discharge typical of spindle oscillations (Fig. 1(C), 1 shock); stimulation with >5 shocks, however,

Fig. 2. Control of thalamic oscillations by corticothalamic feedback. (A) Scheme of the thalamic slice. Corticothalamic axons run in the optic radiation (OR) and connect thalamocortical cell in the LGN layers and GABAergic interneurons in the perigeniculate nucleus (PGN). Bipolar stimulating electrodes were placed in the OR (OT: optic tract). (B) Weak (single shock) stimulation at a latency of 20 ms after the detection of multiunit bursts activity (upper trace). Lower trace: smooth integration of the multiunit signal. (C) A 7 Hz control spindle is slowed down to a robust 3 Hz oscillation by the feedback stimulation (5 shocks; 100 Hz; 20 ms delay). Figure modified from Ref. [1].

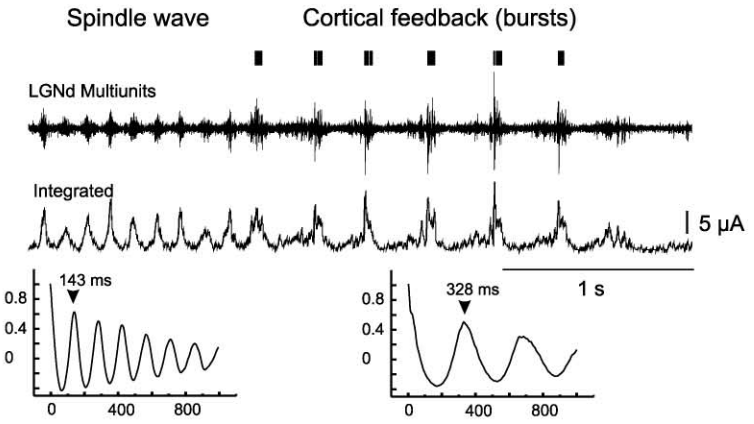
(A)


Feedback stimulation
of corticothalamic axons
OR
PGN
LGN
OT
dLGN slice
0,5 mm

(B)


Cortical feedback (single shocks)
LGNd
Multiunits
Integrated
1 s
161 ms
0.8
0.4
0
0
400
800

(C)


Spindle wave
Cortical feedback (bursts)
LGNd Multiunits
Integrated
5 μA
1 s
143 ms
328 ms
0.8
0.4
0
0
400
800

qualitatively changed the pattern of bursting and led to slow (2–4 Hz) oscillations with higher synchrony (Fig. 1(C), 6 shocks); the latter pattern was dependent on $GABA_B$ receptors (Fig. 1(C), no $GABA_B$). The model thus predicts that, if a single LGN cell triggers the stimulation of corticothalamic feedback, a slower and more synchronized oscillation can be evoked in thalamic circuits.

3.2. Corticothalamic control of oscillations in thalamic slices

The same feedback paradigm was investigated in ferret thalamic slices comprising LGN and PGN layers. Similar to the model, we varied the strength of stimuli to corticothalamic fibers. Weak stimuli (1–2 shocks at 100 Hz) did not significantly perturb the spindle rhythm observed in control conditions (Fig. 2(B)). A qualitatively different behavior was observed when stimuli consisted of high-frequency bursts of at least 4 shocks (typically 5–6 shocks at 100–140 Hz): the oscillation frequency slowed down to a robust 2–4 Hz (2.82 ± 0.67 Hz versus 6.47 ± 0.65 Hz in control; $n = 16$ slices), as demonstrated in extracellular multiunit ($n = 6$; Fig. 2(C)) or extracellular single unit recordings ($n = 3$; not shown). Intracellular recordings also showed a disappearance of IPSPs at 6–10 Hz ($n = 7$; not shown), consistent with a population rhythm of 2–4 Hz.

Two additional properties were demonstrated. First, the 2–4 Hz oscillations elicited by strong feedback are characterized by a larger synchrony compared to spindle oscillations [1,4] in perfect accordance with the model (Fig. 1(C)). This increase of synchrony was demonstrated by measuring the integrated activity of multiunit recordings during the two oscillation types (see details in Ref. [1]). Second, we investigated the receptor types involved in generating the slow 2–4 Hz oscillation. Pharmacological manipulations showed that the ability of corticothalamic feedback to force the thalamic circuit into 2–4 Hz synchronized oscillations was suppressed after antagonizing $GABA_B$ receptors [1,4], consistent with the model (Fig. 1(C)).

Because both interneurons and thalamic reticular cells are possible sources of $GABA_B$ currents [6,24], we compared these two cell types during the stimulation of corticothalamic fibers. Intrageniculate interneurons displayed moderate discharge patterns (Fig. 3, left panels), which contrasted with the burst discharges displayed by perigeniculate neurons (Fig. 3, right panels). At rest, the discharge of interneurons in response to high-frequency bursts of cortical input stimulation (5 shocks; 100 Hz) or to a depolarizing drive is much weaker than that of PGN cells (Fig. 3(B) and (C)). On the basis of these response patterns, and because the activation of $GABA_B$ responses requires high-frequency bursts of presynaptic spikes [9,17,22], PGN cells seem principally responsible for $GABA_B$ IPSPs, although a possible participation of interneurons cannot be excluded. We conclude that the cortical-induced hypersynchronous oscillations are mostly mediated by LGN–PGN loops, in agreement with the model.

3.3. Mechanisms underlying the control of thalamic oscillation by cortical feedback

To further investigate possible cellular mechanisms to explain the present findings, we returned to the model to characterize the increase of synchrony by calculating the

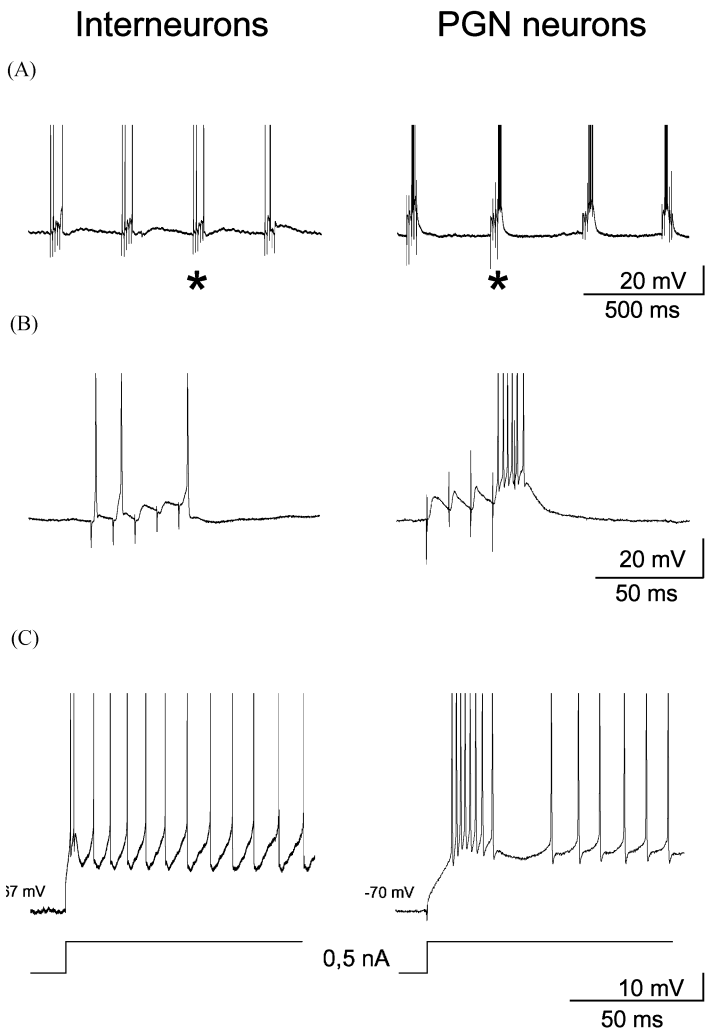


Fig. 3. Response properties of interneurons versus thalamic reticular neurons to corticothalamic input. (A) Intracellular recording of a local interneuron (left column) and a thalamic reticular (PGN) neuron (right column) during OR stimulation imposed periodically without feedback (5 shocks; 100 Hz; ~300 ms interstimulus interval). (B) Expanded details of the discharges labeled by * in (A). (C) A depolarizing pulse (0.5 nA) injected in the cells induces a doublet of spikes followed by a tonic discharge in the interneuron (left) and a sustained burst of spikes in the PGN neuron (right). Spikes are truncated for clarity.

total number of spikes fired by the LGN population (Fig. 1(D)). At the onset of the feedback (arrow, 6 shocks at 100 Hz), the spindle rhythm (approx. 10 Hz) turned into a slower frequency (about 3 Hz) characterized by a marked increase of synchrony. This behavior showed a similar dependence as the experiments in intensity, number of

shocks, and delay. It was always possible to obtain a behavior consistent with all experiments under two conditions: first, the AMPA-mediated cortical EPSPs had to be significantly stronger on PGN cells compared to that of LGN cells (about 5–20 times), consistent with a previous study [11]. Second, the activation of $GABA_B$ receptors needed to be nonlinear ($GABA_B$ IPSPs are negligible with a few presynaptic spikes, but are strong with a large number of presynaptic spikes), consistent with previous studies [9,17,22].

Finally, the model was used to evaluate the "output" of the thalamus in response to corticothalamic feedback. The total average number of spikes evoked in LGN cells by feedback stimulation was computed for different stimulus strength (Fig. 1(E)). From 1 to 4 shocks, there was a slight tendency to increase synchrony, but the number of spikes stayed low (less than one spike on average per LGN cell). However, at 5 shocks and higher, thalamic cells displayed a qualitatively different firing pattern with nearly all cells firing in the same phase (see also Fig. 1(C)). Thus, the model predicts that thalamic circuits can provide at least two qualitatively different types of output in response to cortical stimuli. Moderate corticothalamic stimuli evoke a relatively moderate thalamic response, whereas with strong corticothalamic stimuli, thalamic circuits will return to the cortex a volley of action potentials of greater synchrony and therefore of a greater impact on their cortical targets.

4. Discussion

Experiments and models indicate that corticothalamic feedback inputs are capable of selecting between two types of oscillations in intact thalamic circuits. Mild feedback entrains the circuit into the 6–14 Hz spindle rhythm while strong feedback stimuli generate a slower oscillation (2–4 Hz) of higher synchrony.

The mechanism underlying the feedback control of thalamic oscillations seem to involve the reticular (PGN) nucleus and its projection on relay cells. Intracellular recordings of PGN cells and computational models indicate that cortical EPSPs on PGN neurons are powerful enough to overcome the lateral inhibition between these cells (Fig. 1(C), insets). This powerful effect is consistent with morphological studies showing that corticothalamic synapses are very dense on reticular neurons [19]. Consequently, strong EPSPs from the cortex can elicit prolonged burst discharges in PGN neurons, which in turn activate a full-blown $GABA_B$-mediated component of the IPSPs in LGN cells. The rebound of LGN cells at the offset of these $GABA_B$ IPSPs re-excites the feedback and the same cycle repeats at a frequency of 2–4 Hz.

These findings demonstrate that the cortex has the possibility of sending a "reset" signal to the thalamus, bringing nearly all thalamic neurons into synchrony. This type of interaction has implications in the genesis of pathological oscillatory behavior, such as absence epilepsy. As suggested previously [8], a disinhibition in the cortex can result in excessive discharges of the thalamically-projecting layer VI neurons, resulting in a too strong corticothalamic feedback that can "force" thalamic circuits in a slow hypersynchronous oscillatory mode. The present results are consistent with such a scenario and predict that an excessive discharge of layer VI cells could potentially

entrain the entire thalamocortical system in synchronized oscillations at around 3 Hz. This scenario is consistent with a number of observations in experimental models of absence seizures showing that the thalamus is essential for generating seizure activity [7,15]. In particular, the observation that injection of convulsants limited to the cortex is very effective in generating seizures, but only if the thalamus is intact [16,23], is naturally explained by the present findings.

Acknowledgements

Research supported by CNRS, the Medical Research Council of Canada and the National Institutes of Health.

References

[1] T. Bal, D. Debay, A. Destexhe, Cortical feedback controls the frequency and synchrony of oscillations in the visual thalamus, J. Neurosci. 20 (2000) 7478–7488.
[2] T. Bal, M. von Krosigk, D.A. McCormick, Synaptic and membrane mechanisms underlying synchronized oscillations in the ferret lateral geniculate nucleus in vitro, J. Physiol. 483 (1995) 641–663.
[3] T. Bal, M. von Krosigk, D.A. McCormick, Role of the ferret perigeniculate nucleus in the generation of synchronized oscillations in vitro, J. Physiol. 483 (1995) 665–685.
[4] H. Blumenfeld, D.A. McCormick, Corticothalamic inputs control the pattern of activity generated in thalamocortical networks, J. Neurosci. 20 (2000) 5153–5162.
[5] D. Contreras, A. Destexhe, T.J. Sejnowski, M. Steriade, Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback, Science 274 (1996) 771–774.
[6] V. Crunelli, M. Haby, D. Jassik-Gerschenfeld, N. Leresche, M. Pirchio, Cl^-- and K^+-dependent inhibitory postsynaptic potentials evoked by interneurones of the rat lateral geniculate nucleus, J. Physiol. 399 (1988) 153–176.
[7] L. Danober, C. Deransart, A. Depaulis, M. Vergnes, C. Marescaux, Pathophysiological mechanisms of genetic absence epilepsy in the rat, Prog. Neurobiol. 55 (1998) 27–57.
[8] A. Destexhe, Spike-and-wave oscillations based on the properties of $GABA_B$ receptors, J. Neurosci. 18 (1998) 9099–9111.
[9] A. Destexhe, T.J. Sejnowski, G-protein activation kinetics and spill-over of GABA may account for differences between inhibitory responses in the hippocampus and thalamus, Proc. Natl. Acad. Sci. 92 (1995) 9515–9519.
[10] A. Destexhe, T. Bal, D.A. McCormick, T.J. Sejnowski, Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices, J. Neurophysiol. 76 (1996) 2049–2070.
[11] A. Destexhe, D. Contreras, M. Steriade, Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells, J. Neurophysiol. 79 (1998) 999–1016.
[12] A. Destexhe, M. Mainen, T.J. Sejnowski, Kinetic models of synaptic transmission, in: C. Koch, I. Segev (Eds.), Methods in Neuronal Modeling, MIT Press, Cambridge MA, 1998, pp. 1–26.
[13] A. Erisir, S.C. VanHorn, S.M. Sherman, Relative numbers of cortical and brainstem inputs to the lateral geniculate nucleus, Proc. Natl. Acad. Sci. 94 (1997) 1517–1520.
[14] A. Erisir, S.C. VanHorn, M.E. Bickford, S.M. Sherman, Immunocytochemistry and distribution of parabrachial terminals in the lateral geniculate nucleus of the cat: a comparison with corticogeniculate terminals, J. Comput. Neurol. 377 (1997) 535–549.
[15] P. Gloor, R.G. Fariello, Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy, Trends Neurosci. 11 (1988) 63–68.

[16] P. Gloor, L.F. Quesney, H. Zumstein, Pathophysiology of generalized penicillin epilepsy in the cat: the role of cortical and subcortical structures. II. Topical application of penicillin to the cerebral cortex and subcortical structures, Electroencephalogr. Clin. Neurophysiol. 43 (1977) 79–94.
[17] U. Kim, M.V. Sanchez-Vives, D.A. McCormick, Functional dynamics of GABAergic inhibition in the thalamus, Science 278 (1997) 130–134.
[18] X.B. Liu, C.N. Honda, E.G. Jones, Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat, J. Comput. Neurol. 352 (1995) 69–91.
[19] X.B Liu, E.G. Jones, Predominance of corticothalamic synaptic inputs to thalamic reticular nucleus neurons in the rat, J. Comput. Neurol. 414 (1999) 67–79.
[20] A.M. Sillito, H.E. Jones, G.L. Gerstein, D.C. West, Feature-linked synchronization of thalamic relay cell firing induced by feedback from the cortex, Nature 369 (1994) 479–482.
[21] M. Steriade, M. Deschenes, The thalamus as a neuronal oscillator, Brain Res. Rev. 8 (1984) 1–63.
[22] A.M. Thomson, A. Destexhe, Dual intracellular recordings and computational models of slow IPSPs in rat neocortical and hippocampal slices, Neuroscience 92 (1999) 1193–1215.
[23] M. Vergnes, C. Marescaux, Cortical and thalamic lesions in rats with genetic absence epilepsy, J. Neural Transmission 35 (Suppl.) (1992) 71–83.
[24] M. von Krosigk, T. Bal, D.A. McCormick, Cellular mechanisms of a synchronized oscillation in the thalamus, Science 261 (1993) 361–364.