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

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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. © 2001 Elsevier Science B.V. All rights reserved.

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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

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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).
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.
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].

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 $\rightarrow$ PGN was mediated by AMPA receptors, while the PGN $\rightarrow$ 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.

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,
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.

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.

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$_{\beta}$ receptors needed to be nonlinear (GABA$_{\beta}$ 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$_{\beta}$-mediated component of the IPSPs in LGN cells. The rebound of LGN cells at the offset of these GABA$_{\beta}$ 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
entain 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.

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References


