

Sleep and Sleep States: Thalamic Regulation

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Introduction

During slow-wave sleep, brain activity is dominated by oscillations, such as delta oscillations and slower oscillations. The thalamus, together with the cortex, participates in generating and sustaining these oscillations. Delta waves were observed in the isolated cortex *in vivo* by Frost and colleagues in 1966, and delta-wave activity has been found in the isolated thalamus as well in thalamic slices, although these are more regular than delta waves *in vivo*. The latter studies demonstrated that this form of delta-wave activity is generated intrinsically by the interplay of I_T and I_h currents in thalamocortical (TC) neurons. Slow oscillations (<1 Hz) can be generated by the cortex; they were observed in cortical slices by Sanchez-Vives and McCormick in 2000. A similar type of oscillation has also been observed by the group of V Crunelli to be an intrinsic property of thalamic neurons when metabotropic receptors are stimulated.

Spindle oscillations, which are mostly visible in the early stages of sleep (stage II in humans), are the best-studied sleep oscillation and are generated by thalamic circuits under physiological conditions. In contrast to delta and slow oscillations, for which cortical generators also exist, spindles are generated exclusively in the thalamus. We focus here on sleep spindles, their genesis by thalamic networks, how these oscillations are distributed across the entire TC system, and how they are modulated.

In the human electroencephalogram (EEG), spindle oscillations are grouped in short 1–3 s periods of 7–14 Hz oscillations, organized within a waxing-and-waning envelope, that recur periodically every 10–20 s. In cats and rodents, spindle waves of similar characteristics appear during slow-wave sleep and are typically more prominent at sleep onset. They are enhanced by some anesthetics, such as barbiturates, which, when administered at an appropriate dose, generate an EEG dominated by spindles. In ferret thalamic slices, spindle oscillations occur spontaneously. This *in vitro* model of spindle waves has made it possible to precisely characterize the ionic mechanisms underlying spindle oscillations.

The first indication that spindles could originate outside the cerebral cortex was from Bishop in 1936, who showed that rhythmical activity was suppressed in the cerebral cortex following destruction of its connections with the thalamus. In 1938, Bremer showed that rhythmical activity is still present in the white matter following destruction of the cortical mantle. Later, Adrian in 1941 and Morison and Bassett in 1945 observed that spindle oscillations persist in the thalamus on removal of the cortex, providing firm experimental evidence that these oscillations originate in the thalamus. These experiments led to the development of the thalamic pacemaker hypothesis, according to which rhythmic activity is generated in the thalamus and communicated to the cortex, where it entrains cortical neurons and is responsible for the rhythmical activity observed in the EEG.

Thalamic Pacemakers for Sleep Spindle Oscillations

The first cellular mechanism for the genesis of spindle oscillations was proposed by Andersen and Eccles in 1962. From intracellular recordings from TC relay neurons during spindles, they reported that TC cells fired bursts of action potentials interleaved with inhibitory postsynaptic potentials (IPSPs). They suggested that TC cells fire in response to IPSPs (postinhibitory rebound), which was later demonstrated to be a characteristic electrophysiological feature of thalamic cells by Jahnsen and Llinas. Andersen and Eccles suggested that the oscillations arise from the reciprocal interactions between TC cells and inhibitory local-circuit interneurons. This mechanism was later incorporated into a computational model that provided a phenomenological description of the inhibitory rebound.

The mechanism proposed by Andersen and Eccles was seminal but not entirely correct because reciprocal connections between TC cells and thalamic interneurons have never been observed in anatomical studies. It was later found by Scheibel and Scheibel that the thalamic reticular (RE) nucleus, a sheetlike structure of inhibitory neurons surrounding the thalamus, could provide the inhibition of TC cells and that TC-RE loops could underlie the recruitment phenomena and spindle oscillations. They predicted that the output of the RE nucleus should be inhibitory and that the inhibitory feedback from RE cells onto TC cells should be critical for the genesis of thalamic rhythmicity. This hypothesis was supported by the observation that the pattern of firing of RE neurons was tightly correlated with IPSPs in TC neurons.

Several critical experiments by the group of Steriade firmly established the involvement of the RE nucleus in the generation of spindles in cats *in vivo*. The typical intracellular features of spindle oscillations in the two thalamic cell types is shown in Figure 1(a). By using intracellular or extracellular experiments, it was shown that (1) cortically projecting thalamic nuclei lose their ability to generate spindle oscillations if deprived of input from the RE nucleus and (2) the isolated RE nucleus can itself generate rhythmicity in the spindle frequency range.

Thus, thalamic rhythmicity can be explained by three different mechanisms: the TC interneuron loops of Andersen and Eccles, the TC-RE loops of Scheibel and Scheibel, and the RE pacemaker hypothesis of Steriade (although Steriade's work also demonstrated the importance of the cortex; see the section titled 'Dialog between thalamus and cortex: emergence of large-scale synchrony'). The introduction of an *in vitro* model of spindle waves in ferrets by McCormick's group (Figure 1(b)) supported the second of these mechanisms. Slices of the visual thalamus that contain the dorsal (lateral geniculate nucleus

(LGN)) and reticular nuclei (perigeniculate nucleus (PGN)) as well as the interconnections between them generated spindles spontaneously, confirming earlier experimental evidence for the genesis of spindles in the thalamus.

The *in vitro* preparation allowed detailed pharmacological investigation of the ionic currents and synaptic receptors underlying the spindle oscillations. The spindle waves disappeared after the connections between TC and RE cells were severed, consistent with the mechanism based on intrathalamic TC-RE loops proposed by Scheibel and Scheibel. This *in vitro* experiment also confirmed the observation that the input from RE neurons is necessary to generate spindles, as found by Steriade's group in 1985. However, the RE nucleus maintained *in vitro* did not generate oscillations without connections with TC cells, in contrast with the observation of spindle rhythmicity in the isolated RE nucleus *in vivo* by Steriade's group in 1987.

Thus, *in vitro* experiments appear to support a mechanism by which oscillations are generated by the TC-RE loop, in contrast with the RE pacemaker hypothesis. Computational models suggested a way to

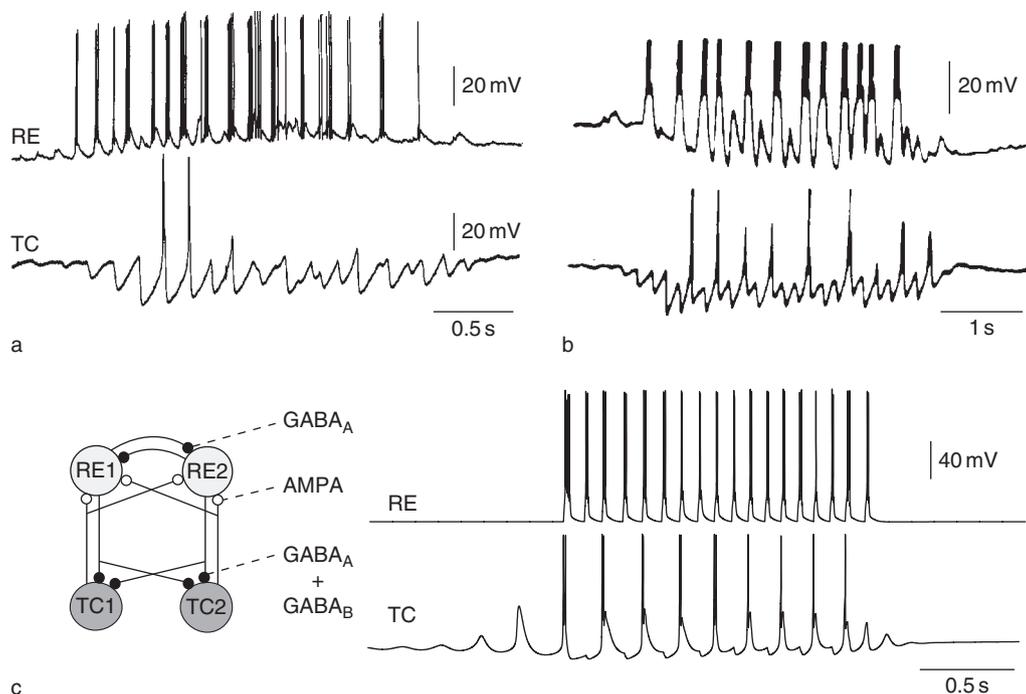


Figure 1 Spindle oscillations in thalamic circuits: (a) *in vivo* intracellular experiments in cats under barbiturate anesthesia, showing the activity of thalamocortical (TC) and thalamic reticular (RE) cells during spindle waves; (b) *in vitro* intracellular experiments in ferret visual thalamic slices, showing the activity of the same type of thalamic neurons during spindle waves; (c) computational model of spindle waves generated by TC-RE interactions. The left drawing in (c) shows a simple circuit, consisting of two TC and two RE cells interconnected with glutamatergic (AMPA) and GABAergic receptors (GABA_A and GABA_B). The right drawing in (c) shows the activity of two model neurons during simulated spindle waves. AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ -aminobutyric acid. (a) Modified from Steriade M and Deschênes M (1984) The thalamus as a neuronal oscillator. *Brain Research Review* 8: 1–63. (b) Modified from von Krosigk M, Bal T, and McCormick DA (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261: 361–364. (c) Modified from Destexhe A, Bal T, McCormick DA, and Sejnowski TJ (1996) Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices. *Journal of Neurophysiology* 76: 2049–2070.

reconcile these apparently contradictory experimental observations. Models showed that both types of rhythmicities are possible and suggested ways to reconcile the experiments. First, different modeling studies found that oscillations very similar to isolated RE preparation *in vivo* could be generated by networks of RE cells. The oscillations were generated by the interaction between the rebound properties of RE cells, as provided by the T-type Ca^{2+} current I_T , and γ -aminobutyric acid (GABA)-mediated IPSPs, consistent with experiments. Second, several modeling studies found that spindle oscillations with characteristics identical to those in the *in vitro* preparation could be generated from TC-RE loops (Figure 1(c)). In this case, the oscillations were dependent on I_T -mediated rebound properties in the TC cells and GABA-mediated IPSPs, together with excitatory

postsynaptic potential (EPSP)-evoked bursts in RE cells. Third, it has been proposed that the differences observed between spindles *in vitro* and *in vivo* could be explained by the limited connectivity between the RE neurons in the slice and/or insufficient levels of neuromodulation in the slice needed to maintain isolated RE oscillations.

Dialog between the Thalamus and Cortex: Emergence of Large-Scale Synchrony

The initiation and distribution of spindle oscillations in large circuits was investigated more recently by using multiple recordings *in vivo* and *in vitro* (Figures 2(a) and 2(c)). Spindle oscillations *in vitro* show traveling wave patterns, with the oscillation typically starting on one side of the slice and propagating

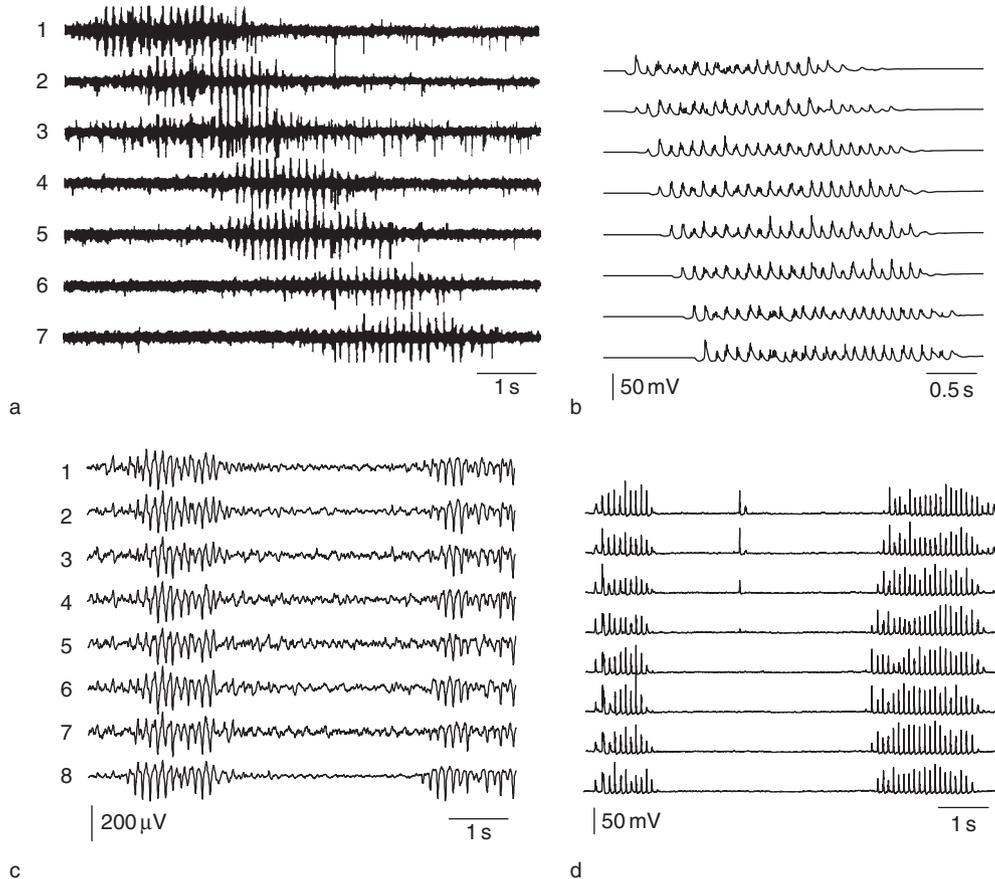


Figure 2 Control of spindle oscillations by the cerebral cortex: (a) multisite extracellular recordings *in vitro* showing the propagating activity of spindle waves in the visual thalamic slice; (b) model of propagating spindle wave activity in thalamic networks with topographic connectivity; (c) multisite extracellular recordings in the thalamus of cats *in vivo* showing the large-scale synchrony of spindle waves in the intact thalamocortical (TC) system; (d) model of the TC network showing large-scale synchrony. (a) Modified from Kim U, Bal T, and McCormick DA (1995) Spindle waves are propagating synchronized oscillations in the ferret LGNd *in vitro*. *Journal of Neurophysiology* 74: 1301–1323. (b) Modified from Destexhe A, Bal T, McCormick DA, and Sejnowski TJ (1996) Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices. *Journal of Neurophysiology* 76: 2049–2070. (c) Modified from Contreras D, Destexhe A, Sejnowski TJ, and Steriade M (1996) Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. *Science* 274: 771–774. (d) Modified from Destexhe A, Contreras D, and Steriade M (1998) Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *Journal of Neurophysiology* 79: 999–1016.

to the other side at a constant propagation velocity (Figure 2(a)). In contrast to thalamic slices, the intact TC system *in vivo* does not display such clear-cut propagation, but spindle oscillations are remarkably synchronized over extended thalamic regions and show very limited traveling-wave activity (Figure 2(c)), in agreement with early observations. Moreover, a study by Contreras and colleagues in 1996 showed that large-scale synchrony was lost when the cortex was removed, suggesting that, although the oscillation is generated by the thalamus, its synchrony depends on the cortex. However, cutting intracortical connections has no effect on large-scale synchrony, so cortical connections are not responsible for organizing the synchrony of sleep spindles.

The mechanisms for large-scale synchrony were investigated by computational models by first simulating the propagating properties found in slices (Figure 2(b)). These models assumed a topographic connectivity between TC and RE layers and could generate traveling spindle waves consistent with *in vitro* data. Second, a model by Destexhe and colleagues in 1998 simulated TC networks with bidirectional interactions between the cortex and thalamus and showed that all experiments could be reproduced under the assumption that the cortex recruited TC cells primarily through inhibition. This inhibitory-dominant cortical feedback to the thalamus is consistently observed experimentally and can explain large-scale synchrony by the mutual recruitment of thalamic and cortical networks (Figure 2(d)). The same mechanism can also explain the genesis of absence-type of epileptic seizures when the excitability of cortical neurons is too high. The concept of cortical control of thalamic spindle oscillations can be generalized to other oscillation types, and it was proposed by Steriade that the slow oscillation organizes spindle oscillations, delta oscillations, and more complex patterns such as K-complexes.

Control of Sleep Oscillations by Neuromodulators

Neuromodulators such as acetylcholine (ACh), norepinephrine, (NE), serotonin, (5-HT), histamine (HA), and glutamate abolish the low-frequency rhythms in TC systems during sleep. In the thalamus, where both the relay neurons and the reticular thalamic cells are hyperpolarized during sleep, the activation of the neuromodulatory systems depolarizes the thalamic cells by 5–20 mV, inactivating the low threshold Ca^{2+} current and inhibiting bursting. The transition to tonic firing enhances the participation of sensorimotor processing, which is blocked during sleep.

Conclusion

The thalamus shifts during sleep from a tonic mode, suitable for relaying information from the periphery to the cortex, to a rhythmic mode that generates activity and produces highly spatially and temporally coherent states through interactions with the cortex. During sleep, the feedback connections from the cortex to the thalamus become highly effective in globally coordinating activity in the thalamus. Thus, the thalamus becomes a mirror during sleep, linking distant parts of the cortex. This could be important for maintaining and adjusting the overall balance of activity in the cortex.

See also: Sleep and Sleep States: Hypothalamic Regulation; Sleep and Sleep States: Phylogeny and Ontogeny; Sleep Oscillations and PGO Waves; Sleep Oscillations.

Further Reading

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