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Sleep, epilepsy and thalamic reticular inhibitory neurons

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Thalamic reticular neurons release the potent inhibitory neurotransmitter GABA and their main targets are thalamocortical neurons in the dorsal thalamus. This article focuses on two topics: (i) the role of thalamic reticular neurons in the initiation of spindles, a hallmark oscillation during early sleep stages; and (ii) the reticular-induced inhibition of thalamocortical neurons during cortically generated spike-wave seizures. Although hotly debated during the past decade, the idea of spindle generation by a network of GABAergic reticular neurons was recently supported by *in vivo* and *in computo* studies demonstrating interactions between inhibitory reticular neurons that lead to spindle sequences. During spike-wave seizures and electrical paroxysms of the Lennox-Gastaut type, which arise in the neocortex, reticular neurons are powerfully excited through corticofugal projections and they produce prolonged inhibitory postsynaptic potentials in thalamocortical neurons. Thus, GABAergic reticular neurons are crucial in the generation of some sleep rhythms, which produce synaptic plasticity, and in inhibiting external signals through thalamocortical neurons, which leads to unconsciousness during absence epilepsy.

Introduction

The thalamic reticular (RE) nuclear complex consists of a neuronal sheet that covers most of the rostral, lateral and ventral parts of the thalamus. RE inhibitory cells release GABA and their interconnected networks are particularly well suited for the generation of spindle oscillations (7–14 Hz) that characteristically appear during early stages of sleep and can occur even in the isolated RE nucleus [1]. RE neurons control information processing through their major targets, thalamocortical (TC) neurons [2]. The GABAergic RE neurons form reciprocal neuronal loops with glutamatergic TC cells, their major source of excitation is the neocortex [3], and they are inhibited by ACh [4] released from projections of the brainstem reticular core and basal forebrain [5].

RE neurons have long dendrites, which possess vesicle-containing appendages that form synapses on the dendrites of neurons in the same nucleus [6,7]. Dendrodendritic synapses have been definitely recognized in cats,

although their existence in monkeys is controversial and they have not yet been described in rats. Besides chemical synapses, RE neurons are electrically coupled [8]. Spikelets, the electrophysiological correlates of gap junctions, are fast-rising and fast-decaying events, significantly different from excitatory postsynaptic potentials (EPSPs): in spikelets, the rising phase peaks at 0.5 ms and the decaying phase peaks at 1 ms, whereas the same phases in EPSPs peak at 1 ms and 4 ms, respectively [9]. Another difference is that spikelets cannot elicit full action potentials during states of membrane depolarization at which EPSPs lead to cell firing. Spikelets could also be distinguished from fast prepotentials that are usually considered as dendritic spikes triggered by synaptic stimuli [9]. Experimental and computational models of RE neurons predicted that gap junctions between these neurons could mediate the spread of low-frequency activity within the nucleus [9], with the implication that both chemical synapses and electrotonic coupling among RE neurons have important roles in the generation and synchronization of low-frequency activities in the thalamus, such as sleep spindles.

One of the intrinsic properties of RE neurons is the low-threshold spike (LTS) that is de-inactivated by membrane hyperpolarization [10]. The LTS is localized mainly in the dendrites of RE neurons [11] and is triggered by corticofugal volleys [12]. The LTS gives rise to fast spikes that produce long-lasting inhibitory postsynaptic potentials (IPSPs) mediated by GABA_A and GABA_B receptors in TC neurons (Figure 1a). The bursts of action potentials that crown LTSs typically occur during natural slow-wave sleep and are replaced by tonic, single-spike firing during brain-activated states [13]. Another intrinsic property in a subgroup of RE neurons is membrane bistability, which is strongly voltage-dependent (only present under resting conditions) and consists of two alternate membrane potentials, separated by ~17–20 mV [14]. Whereas non-bistable RE neurons fire rhythmic spike bursts during spindles, bistable RE neurons fire tonically, with burst modulation, throughout spindle sequences. Target TC cells present various patterns of spindling that reflect the membrane bistability or non-bistability in RE neurons (Figure 2 and Box 1).

This article will focus on two sets of data relevant to two hotly debated issues: the generation of sleep spindles in the isolated RE nucleus and the inhibition of TC neurons during cortically generated spike-wave seizures.

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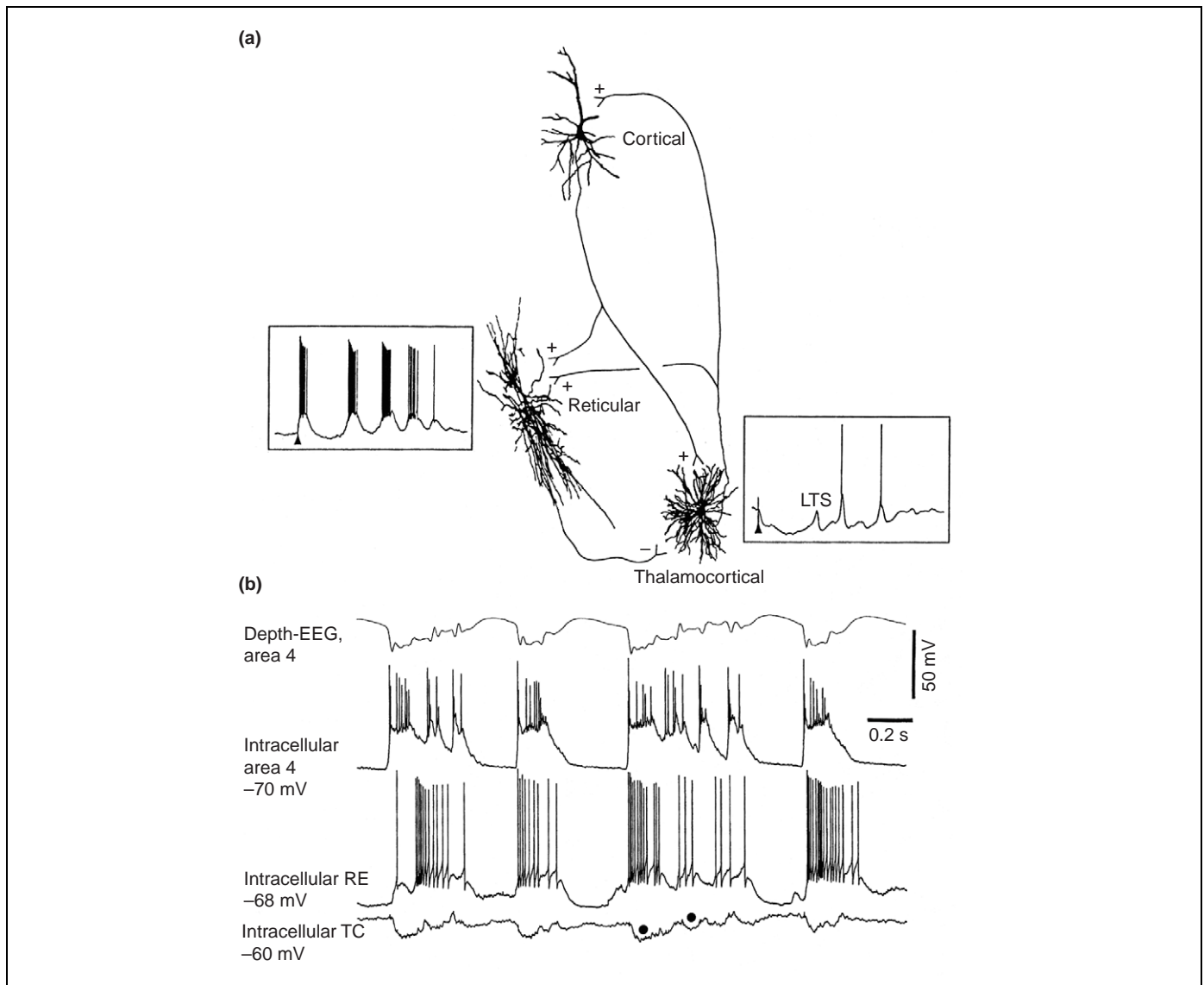


Figure 1. Functional relationships between corticothalamic, thalamic reticular (RE) and thalamocortical (TC) neurons. **(a)** Three neurons (cortical, RE and TC) were intracellularly recorded and stained in cats. Excitation and inhibition are indicated by plus and minus symbols, respectively. For simplicity, local-circuit inhibitory neurons in cortex and thalamus are not illustrated. Insets represent the response of RE and TC neurons to cortical stimulation (arrowheads point to stimulus artifacts). The GABAergic RE neuron responded to cortical stimulation with a high-frequency spike burst, followed by a sequence of spindle waves on depolarization (membrane potential -68 mV). The TC neuron responded to cortical stimulation (arrowhead) with a biphasic IPSP mediated by GABA_A and GABA_B receptors, leading to a low-threshold spike (LTS) and a sequence of hyperpolarizing spindle waves (membrane potential -70 mV). **(b)** Relationships between cortical (area 4), RE and TC neurons of cats during a spontaneously occurring, cortically generated seizure with polyspike-wave (PSW) complexes at 2 Hz (the cats were under ketamine-xylazine anesthesia). Cortical and TC neurons were recorded simultaneously; the RE neuron was recorded during virtually identical EEG patterns. Note IPSPs in the TC neuron (black circles) in close time relationship with spike bursts fired by the RE neuron, driven by the cortex. Modified from Refs [45,54].

Sleep spindles are initiated and generated in the isolated RE nucleus

The role of RE inhibitory networks in the generation of spindles was originally shown *in vivo* after disconnection from the remaining thalamus [1], and was corroborated by subsequent computational and experimental studies [15–18]. Although some experiments *in vitro* did not record spindles in the isolated RE nucleus [19], this failure was explained by the slicing procedure that cuts the long dendrites of RE neurons, which are crucial in generating the spindle rhythm [20]. Another factor to consider is the necessary condition that, to produce spindles, RE neurons should be slightly depolarized [21] by projections from brainstem monoamine-containing (dorsal raphe and locus coeruleus) neurons [22] or from other activating systems,

such as the cerebral cortex, which are absent in a thalamic slice. Further studies have shown that, rather than being epiphenomena, with little or no functional significance, sleep spindles are involved in synaptic plasticity (Box 1).

Recent experiments *in vivo* support the initiation and generation of spindles in the isolated RE nucleus [23]. Prolonged (200–300 ms) hyperpolarizing potentials preceded spindle sequences in RE cells and were associated with a significant drop in the apparent input resistance, suggesting an active inhibitory process rather than disfacilitation. The reversal potential of these hyperpolarizations was around -100 mV, consistent with the activation of slow K⁺ conductances, and the prolonged hyperpolarizations were sensitive to intracellular QX-314, a blocker of many membrane conductances, including K⁺

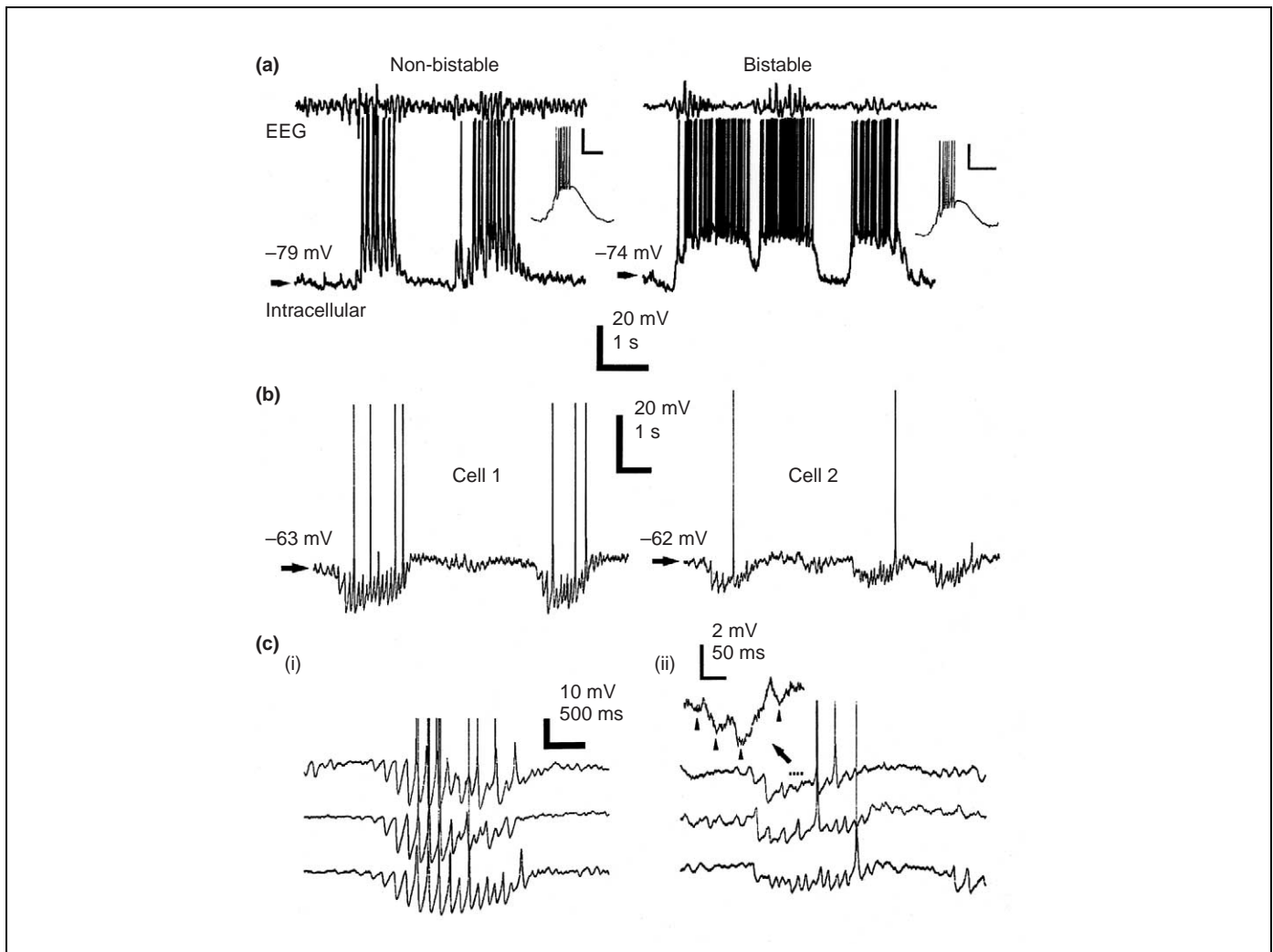


Figure 2. Membrane bistability in RE neurons during spontaneously occurring spindles and different spindling patterns in TC cells, reflecting various firing patterns in RE neurons (recordings made from a cat under barbiturate anesthesia). (a) Cortical EEG and intracellular recordings from two RE neurons. Typical low-threshold spike bursts of each of these RE cells are expanded in the insets. The non-bistable RE neuron fired spike bursts, separated by phasic hyperpolarizations, during spindling. The bistable RE neuron displayed sustained depolarizations throughout spindle waves. Scale bars below the panel apply to the larger traces for both neurons; scale bars in insets represent 50 ms and 20 mV. (b) Intracellular recordings of two TC neurons of the cat ventrolateral nucleus ('cell 1' and 'cell 2') during spindle activity. (c) Expanded traces during one spindle sequence in cell 1 (i) and cell 2 (ii). Note highly regular activity and early rebound bursting in cell 1, reflecting activity in non-bistable (common) RE neurons. For cell 2, which reflects activities in bistable RE neurons, the enlargement of the part of the trace marked by dots shows four IPSPs (arrowheads) at much higher frequency (~ 20 Hz) than the usual frequency range of spindles (Box 1). Modified from Ref. [14].

currents. This implicates of G-protein-dependent K^+ currents, and suggests that the prolonged hyperpolarizations in RE neurons are inhibitory potentials activated by a G protein coupled to second messenger cascades [24]. Because soma depolarization did not increase the amplitude of prolonged hyperpolarizing potentials but rather abolished them [23], the hyperpolarizations preceding spindles could have a dendritic origin, similar to the T-current in RE neurons [11]. Indeed, G-protein-activated, inwardly rectifying K^+ channels mediate dendritic hyperpolarizations [25].

Direct evidence for the origin of the prolonged hyperpolarizations preceding spindles was detected using extracellularly recorded RE neurons in the vicinity of the intracellularly recorded neurons [23], which showed that the firing of the former was temporally related to the hyperpolarization leading to spindles (Figure 3). These data suggest that hyperpolarizations preceding spindles are generated within the RE nucleus. Because corticothalamic excitatory volleys could also elicit such

hyperpolarizations [23,26], we propose that firing in neocortical neuronal pools could excite RE neurons, generating LTSs crowned by spike bursts (at relatively hyperpolarized levels of membrane potential, as occurs in slow-wave sleep), which would induce prolonged hyperpolarizations in adjacent and/or distant RE neurons through dendrodendritic GABAergic synapses [6,7] and electrical coupling [8,9]. The inhibitory actions of RE cells and rebound spike bursts in TC cells are responsible for the transfer of spindles to the cortex [20]. The demonstration of prolonged hyperpolarizations that lead to spindles and are generated locally in the RE nucleus is in line with the original proposal that spindles are initiated within the pace-making GABAergic RE nucleus [1].

RE-induced inhibition of TC neurons during cortical spike-wave seizures

Sequences of paroxysmal spike-wave (SW) and polyspike-wave (PSW) complexes at ~ 3 – 4 Hz are present in absence

Box 1. Sleep spindles

Spindles appear during early stages of sleep. They are generated in the thalamus even after complete decortication [55]. However, their synchronization and virtually simultaneous occurrence over widespread thalamic and cortical territories of animals and humans require corticothalamic feedback [56]. *In vivo* [57–59] and *in vitro* [60] intracellular studies have revealed the cellular mechanisms responsible for spindle generation, demonstrating requirement of the RE nucleus for occurrence of spindles in TC neurons, and showing that prolonged, rhythmic IPSPs in TC cells during spindles are time-locked and generated by spike bursts fired by RE neurons. Any change in the bursting pattern of RE neurons would affect their targets, TC neurons. Thus, the two different patterns during spindles in TC neurons (Figure 2b of the main text) could be related to the actions of non-bistable and bistable RE neurons, respectively. Non-bistable RE neurons fire stronger bursts with higher intra-burst frequencies, which generate deeper and longer IPSPs in TC neurons, giving rise to the usual frequency range of spindles (7–10 Hz). By contrast, IPSPs with lower amplitudes and higher frequencies (up to 20 Hz; Figure 2c, inset) are likely to be generated mainly by single action potentials in RE neurons, because they occur during the depolarizing plateau in bistable RE cells.

Spindles have an important functional role in synaptic plasticity of cortical and thalamic neurons. This topic has been investigated using

thalamic and/or cortical stimulation in the frequency range of sleep spindles (~10 Hz). Dual intracellular recordings *in vivo* from TC and neocortical neurons [61] have shown that both thalamus and neocortex have the neuronal equipment to generate augmenting responses, which grow in size with the second and successive stimuli in a pulse-train, similar to the initial waxing pattern of spindle sequences. Although the augmented response of neocortical neurons follows by ~3 ms the action potentials of simultaneously recorded TC neurons, cortical neurons continue pulsate autonomously within the frequency range of spindles – despite the fact that TC neurons remain hyperpolarized and do not fire [61] because they remain under inhibitory pressure from GABAergic RE neurons. Following rhythmic (10 Hz) volleys to corticothalamic projections, ‘spontaneously’ occurring spike bursts occur in TC neurons, whose pattern and rhythmicity are similar to those of evoked responses, as if the repetition of volleys was imprinted in the ‘memory’ of the corticothalamic network [62]. Intracortical augmenting responses, in addition to naturally occurring spindle sequences, lead to striking potentiation of testing responses evoked by single cortical stimuli, which can last up to 12–15 min [63]. These data led to the hypothesis that spindles, and other low-frequency sleep oscillations generated in thalamocortical systems, might contribute to the consolidation of memory traces acquired during the waking state [64,65] – an idea supported by research in humans [66,67].

epilepsy; lower-frequency (1.5–2.5 Hz) SW and PSW complexes associated with epochs of fast runs (10–20 Hz) characterize hypsarrhythmia that is associated with Lennox–Gastaut syndrome, which is more severe than absence epilepsy and is associated with mental retardation (Box 2). Both these types of seizure occur preferentially during drowsiness or slow-wave sleep, less often during wakefulness, and seemingly never during REM sleep [27]. That such SW seizures – which can (as in human absence epilepsy) begin and end with tonic eye movements – have a focal cortical origin during drowsiness was demonstrated by recording SW complexes at cortical depth in chronically implanted macaque monkeys, sometimes without reflection at the cortical surface [28]. (Box 2). SW complexes are accompanied by neuronal firing during the electroencephalogram (EEG) ‘spike’ and neuronal silence during the EEG ‘wave’ [28]. The focal character of SW and Lennox–Gastaut seizures was also observed in human studies that reported multifocal independent cortical EEG ‘spikes’ [29,30]. SW and PSW seizures, whether associated or not with fast runs, originate focally in cortex but are thereafter transferred to

other cortical sites (through monosynaptic or oligosynaptic pathways) [31] and to the thalamus [32]. Crucial evidence that the neocortex is the minimal substrate for generating SW and/or PSW seizures, whether or not they are associated with fast runs, includes: (i) their presence in the cerebral cortex isolated from thalamus and in cortex after extensive thalamic lesions [33,34]; (ii) their induction by infusion of the GABA_A-receptor antagonist bicuculline in neocortex of ipsilaterally thalamectomized animals [34]; and (iii) their absence after intrathalamic injections of bicuculline, which induce low-frequency, regularly recurring spindle sequences but not SW seizures in cat [34] or rat [35] thalamus *in vivo*. Other experimental and clinical results pointing to the cortical initiation of SW and PSW seizures are summarized in Box 2.

Among various factors that have important roles in triggering SW paroxysmal activity in the neocortex, there are some intrinsic currents, neurons and network operations. Intracellular recordings *in vivo* and computational models showed that the interplay between I_H , $I_{K(Ca)}$ and a persistent Na^+ current ($I_{Na(P)}$) could lead to paroxysmal

Box 2. Spike-wave and Lennox–Gastaut seizures

Spike-wave (SW) complexes at 3–4 Hz in absence seizures, associated with loss of consciousness, are conventionally thought as being ‘suddenly generalized and bilaterally synchronous’, a definition that stemmed from the idea of a ‘centrencephalic’ system, deeply located in the diencephalon and mesencephalon [68] and with presumably bilateral cortical projections. This concept was partly based on experiments showing that SW-like responses (but not self-sustained activity, as should occur in seizures) are evoked in cortex by stimulation of midline thalamic nuclei at 3 Hz [69]. Although the ‘centrencephalic’ system implicated widespread and bilateral projections to the cortex, there are no such thalamic neurons. And midbrain reticular ascending systems disrupt, rather than generate, SW seizures [70]. Although more recent recordings in thalamic slices attempted to resurrect the idea of a thalamic origin of SW seizures, experimental studies *in vivo* and computational modeling led to the conclusion that SW seizures are progressively built up (i.e. not suddenly generalized) in intracortical synaptic networks [71,72], with subsequent excitation

of thalamic RE neurons, leading to inhibition of TC neurons (see main text). Analyses of multiple electrographic leads in animals and humans have also revealed that some SW seizures are locally generated in independent cortical foci, and that synchronization results, at least partially, from intracortical (ipsilateral and callosal) projections [31,41,73,74].

Lennox–Gastaut syndrome is a clinical entity (infantile spasms) that corresponds to the EEG hypsarrhythmia and is characterized by relatively slower SW complexes (1.5–2.5 Hz) intermingled with fast runs at 10–20 Hz. Compared with absence epilepsy this is a more severe epileptic disorder, because it is generally associated with mental retardation, probably due to brain damage. Intracellular recordings of an electrographic pattern in cats, resembling those observed in clinical Lennox–Gastaut syndrome, demonstrate that the onset of many such spontaneously occurring seizures occur focally in the neocortex, only subsequently spreading to the thalamus [75,76].

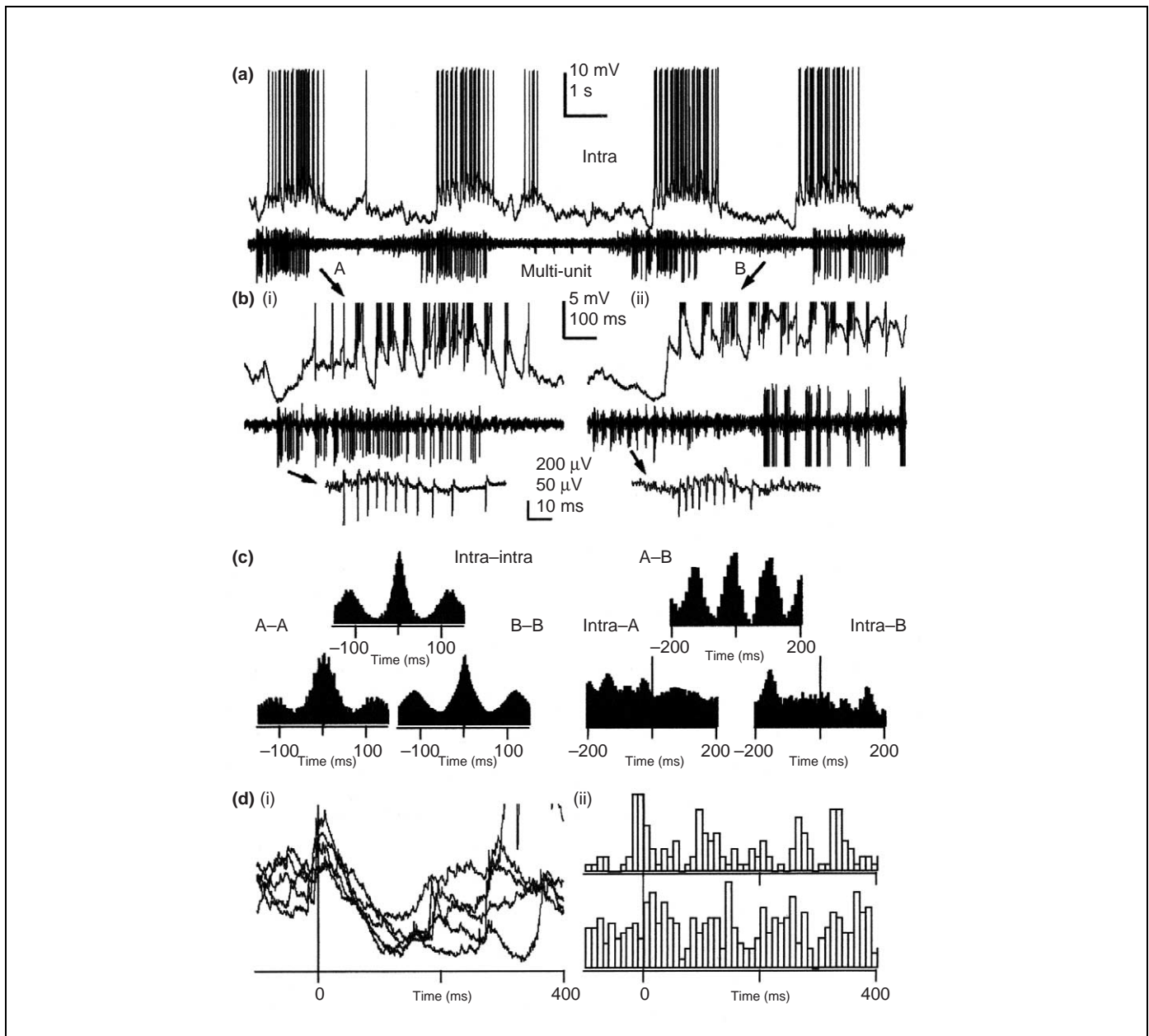


Figure 3. Reticular (RE) neurons fire during the prolonged hyperpolarizations of a simultaneously recorded RE neuron (recordings made from a cat under barbiturate anesthesia). **(a)** Simultaneous recording of intracellular (intra) and extracellular (multi-unit) activities in the RE nucleus. The extracellular electrode was located ~1 mm anterior to the intracellular electrode. Note the presence of two units in the extracellular recording (A and B). **(b)** Expanded traces from epochs in (a), indicated by arrows. (i) The first spindle sequence in (a) for both intracellular and extracellular recordings. Note discharge of one unit (A) during the prolonged hyperpolarizing potential (PHP), preceding spindles. (ii) The last spindle sequence in (a). Note the second unit (B) firing during the PHP. The lower traces and their enlargements depict typical accelerando-decelerando bursts for both units, which identify them as being from RE neurons. **(c)** Autocorrelograms and cross-correlograms of action potentials for intracellular and extracellular recordings. Bin sizes are 1 ms and 5 ms for autocorrelograms and cross-correlograms, respectively. **(d)** Five superimposed traces showing PHPs (i) and correlated discharge in both units for the same period (ii). Time zero was set at the peak of depolarizing potentials preceding PHPs. Bin size, 10 ms. Modified from Ref. [23].

SW oscillations at a frequency of 2–3 Hz [36]. Of the four main classes of cortical long-axon neurons and local interneurons [regular-spiking, fast-spiking, intrinsically-bursting and fast-rhythmic-bursting (FRB)] [37], FRB neurons (20–25% of the total cortical neuronal population) have the highest propensity to develop seizures. This is coupled with the crucial role of FRB neurons in generating ultra-fast oscillations, called ripples (80–200 Hz), which initiate seizures in both animal experiments [38] and humans [39,40]. Thus, during seizures of the Lennox–Gastaut type, which evolve without discontinuity from the slow cortical oscillation [31,32,41], strong ripples occur in

advance of the transition between normal and paroxysmal activity; they are present until the paroxysmal event reaches its full extent, and also at seizure onset in foci where the paroxysmal event is initiated [38]. In addition, spontaneous seizures rarely occur under barbiturate anesthesia, and neocortical ripples are very weak in this condition.

During cortically generated SW and PSW seizures, GABAergic thalamic RE neurons faithfully follow each paroxysmal depolarizing shift of SW complexes (Figure 1b), whereas most TC neurons are steadily hyperpolarized and display phasic IPSPs (Figure 4a),

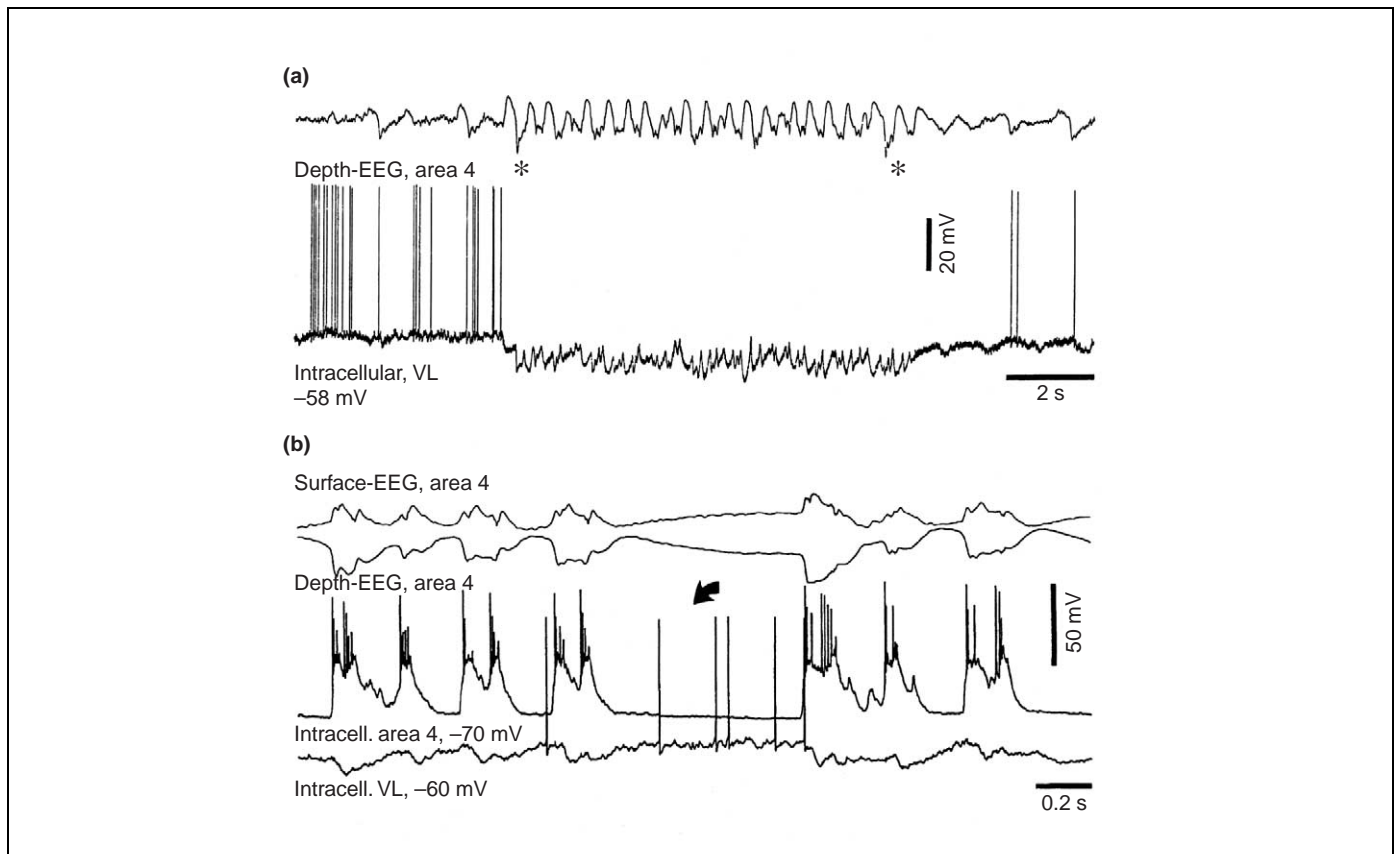


Figure 4. Thalamocortical (TC) neurons are inhibited during a cortically generated spike-wave seizure, and they display phasic IPSPs but not spike bursts (recordings made from a cat under ketamine–xylazine anesthesia). **(a)** Depth-EEG from cortical area 4 and intracellular recording of a TC neuron from the ventrolateral (VL) nucleus. Note hyperpolarization and phasic IPSPs in the neurons throughout cortically generated spike-wave seizure. Asterisks below the EEG trace indicate the onset and end of spike-wave seizures. **(b)** Dual intracellular recordings from an area 4 cortical neuron and a TC neuron from VL nucleus, together with surface-EEG and depth-EEG from cortical area 4. The spike-wave and polyspike-wave seizure developed, without discontinuity, from sleep-like EEG patterns. Note paroxysmal depolarizing shifts in the cortical neuron, and phasic IPSPs related to cortical paroxysmal depolarizing shifts. Also note that, during a brief period of quiescence in cortical seizure (arrow), hyperpolarization of the TC neuron was removed and the neuron fired single action potentials. Modified from Ref. [32] and (M. Steriade and D. Contreras, unpublished).

which do not succeed in de-inactivating Ca^{2+} -dependent LTSs [32,42,43]. The absence of spike bursts in TC neurons after RE-induced hyperpolarization is explained by the repetitive bursts fired by RE neurons during the cortical ‘spike’, which increase the membrane conductance of TC cells to a level that prevents generation of LTSs and spike bursts. Thus, RE neurons driven from the cortex lead to inhibition of TC neurons, and the latter do not produce spike bursts that are normally transferred to cortex. The relationship between cortical SW and/or PSW seizures and steady hyperpolarization with phasic IPSPs in TC neurons is best seen during short periods when the cortical seizure stops and TC cells display depolarization and single-spike firing (Figure 4b).

Recordings of cortical EEG and RE neurons revealed spike bursts in RE neurons that follow each EEG ‘spike’ and increase in duration, from 40 ms during the prior sleep-like pattern to ≥ 200 ms during the seizure [32]. Simultaneous recordings of cortical EEG activity, unit discharges of RE cells, and intracellular activity of a related TC neuron showed IPSPs in the TC neuron, with the same frequency as that displayed by cortical EEG ‘spikes’ and RE-cell spike bursts [32]. In summary, GABAergic RE neurons participate actively during cortically generated SW and PSW seizures *in vivo*. This conclusion is supported by similar data on RE neurons

in a genetic model of absence epilepsy [44]. Consequently, TC neurons are steadily inhibited during seizures that have pure SW complexes in addition to Lennox–Gastaut seizures. Studies using dual intracellular recordings from neocortical and TC neurons *in vivo* showed that, during cortically generated seizures consisting of SW and/or PSW complexes at 2–3 Hz, most TC neurons display steady hyperpolarization in addition to phasic IPSPs, closely related to the EEG ‘spike’ component of cortical SW and PSW complexes; at the end of the cortical seizure, TC neurons fire at high rates, as if they were released from the inhibition that occurred during the seizure [32]. Computational modeling also showed that increasing the inhibitory strength from the GABAergic RE neurons onto TC neurons favors the quiescent mode in the latter [45]. Then, two major types of thalamic neurons undergo opposite influences: RE neurons follow each paroxysmal depolarizing shift of SW complexes, whereas the overwhelming majority of TC neurons are steadily hyperpolarized and display phasic IPSPs that prevent them from transferring spike bursts to the cortex.

Ethosuximide (ETX), which is beneficial in absence epilepsy, was initially described to reduce or block I_T of TC neurons [46,47]; more recent studies have shown that it decreases $I_{\text{Na(P)}}$ but has no effect on I_T [48]. Because I_T is present in neocortical neurons [49,50], and because SW

seizures can occur during prolonged inhibition of TC neurons or even in the absence of the thalamus [32,34], a cortical action of ETX has been proposed [34]. Recently, the cortical block of genetically determined absence seizures was indeed demonstrated by microinfusion of ETX within the cortex, whereas a much less marked response was elicited by even higher dose of drug infusion in the thalamus [51].

Concluding remarks

The RE nucleus is the major inhibitory structure in the thalamus and is interposed in synaptic operations of neocorticothalamic pathways acting on TC neurons. It was assumed that this nucleus has a role in selective attention [52,53], a function that occurs in the adaptive state of wakefulness. During the disconnected state of slow-wave sleep, the RE nucleus generates spindle oscillations, even after its de-afferentation from cortex and the remaining thalamus. This idea, originating from experiments performed during the 1980s [1] was subsequently supported by computational studies that predicted the ability of isolated RE neuronal networks to generate spindles [15–18]. Besides this, recent experiments [23] demonstrated that prolonged hyperpolarizations, associated with a significant drop in input resistance and caused by activation of K^+ conductances, precede and lead to spindles. These hyperpolarizations are generated within the RE nucleus and are due to firing of neighboring or distant RE neurons. As also discussed in this article, SW and PSW seizures that preferentially occur during drowsiness and light slow-wave sleep have a cortical origin. Such seizures are reflected in the thalamus, where they powerfully excite GABAergic RE neurons and consequently inhibit TC neurons. The inhibition with increased membrane conductance in the latter could explain the failed relay of incoming signals from the external world and the unconsciousness during absence epilepsy.

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