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The reticular nucleus revisited: Intrinsic and network properties of a thalamic pacemaker

Pablo Fuentealba, Mircea Steriade *

Laboratoire de Neurophysiologie, Faculté de Médecine, Université Laval, Québec, Que., Canada G1K 7P4

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Abstract

The intrinsic and network properties of thalamic reticular (RE) neurons, which release the potent inhibitory neurotransmitter γ-aminobutyric acid (GABA), endow them with oscillatory properties within the frequency range of sleep spindles (7–15 Hz), a hallmark brain rhythm that characterizes early sleep stages. The original hypothesis that RE neurons are pacemakers of spindles, based on absence of this oscillation in thalamocortical (TC) systems after disconnection from RE nucleus and presence of spindle rhythmicity in the deafferented RE nucleus, is supported by new experimental results in vivo, in vitro and in computo showing that interactions through chemical synapses as well as electrical coupling among inhibitory RE neurons lead to generation and synchronization of spindle sequences within the nucleus. Besides their pacemaking role in spindle generation, RE neurons are crucially implicated in the inhibition of TC neurons during cortically generated spike-wave (absence) seizures, which may explain the obliteration of signals from the external world and unconsciousness during these epileptic fits.

Contents

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; FPP, fast prepotential; GABA, γ-aminobutyric acid; $I_{Na(p)}$, persistent Na^+ current; IPSP, inhibitory postsynaptic potential; LTS, low-threshold spike; NMDA, *N*-methyl-D-aspartate; PDS, paroxysmal depolarizing shift; PSW, polyspike-wave; RE, thalamic reticular; SW, spike-wave; TC, thalamocortical; V_m, membrane potential

* Corresponding author. Tel.: +1 514 343 6370; fax: +1 514 343 2111.
E-mail address: mircea.steriade@phs.ulaval.ca (M. Steriade).

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1. Background

This article addresses a hotly debated issue, namely, to what extent the thalamic reticular (RE) neurons possess intrinsic properties and participate in local network operations allowing them to generate and synchronize a hallmark oscillation that characterizes early sleep stages, spindle waves (7–15 Hz). First discovered during the 1980s, the cardinal role played by the RE nucleus in spindles' induction was shown by abolition of this rhythm in thalamocortical (TC) systems after lesions of RE neurons (Steriade et al., 1985) and, more importantly, by the property of in vivo deafferented RE neurons to generate spindles in the absence of cortex and the remaining thalamus (Steriade et al., 1987a). Those data led us to postulate that RE nucleus is the pacemaker of spindle oscillations. This idea was challenged by the absence of spindles in slices from the posterior (perigeniculate) part of the RE nucleus, maintained in vitro (von Krosigk et al., 1993). However, in a *Science* article (Steriade et al., 1993), the authors of the discrepant results obtained in vivo and in vitro concluded that "spindle oscillations are generated in the reticular thalamic nucleus disconnected from dorsal thalamic and cortical inputs" (p. 684) and, concerning the failure of experiments on RE in vitro slices to find spindles, proposed that "a larger and more intact collection of reticular thalamic cells may be able to generate spindle waves autonomously" (p. 684). More recent experiments and computational studies on isolated RE-cells' networks (see Section 4) congruently led to the conclusion that spindle rhythmicity can be produced within the RE nucleus, without necessarily requiring inputs from TC and cortical neurons. The idea of RE-induction of spindle generation transcends the mechanism of this major sleep oscillation, as it sheds further light on differences between the intact and sliced brain (Steriade, 2001a,b, 2004).

The importance of recent investigations on RE neurons, particularly those that demonstrate the prevalent synaptic weight of neocortical inputs on these cells (Golshani et al., 2001; Jones, 2002), also relates to the role played by RE neurons in inhibiting target TC neurons during cortically generated spike-wave (SW) seizures (Steriade and Contreras, 1995; Crunelli and Leresche, 2002; Steriade, 2003). Seizures with "spike" and "wave" complexes at 3–4 Hz are observed in absence epilepsy, associated with loss of consciousness. The cortical origin of a majority of SW seizures casts doubt on earlier hypotheses claiming that such paroxysms are generated by "centrencephalic systems" (Penfield and Jasper, 1954) and on more recent in vitro data implicating TC neurons in the generation of such seizures (von Krosigk et al., 1993; Huguenard, 1999). The powerful inhibition of TC neurons during SW seizures is also relevant to mechanisms that underlie obliteration of signals from the external world and unconsciousness during such paroxysms.

We first show the place of the RE nucleus in thalamic and cortical circuitry (Fig. 1A). The modulation of RE neurons by some neurotransmitters may partially explain the differences in their behavior between isolated thalamic slices and the intact brain. Next, we deal with the intrinsic properties of RE neurons and their synchronization, which provide the substrate for spindle generation within this nucleus. Finally, we present recent in vivo and in computo data demonstrating the generation of spindles within the RE nucleus and the RE-induced inhibition of TC neurons during SW seizures (see Fig. 1B). Here, we mainly refer to data relevant to the two major topics of this article, spindle oscillations and SW seizures. For other morphological and physiological features of the RE nucleus, such as the topographical organization of different RE sectors and their relations to dorsal thalamic nuclei, the reader may consult previous monographs and reviews (Steriade et al., 1990, 1997; Jones, 2002, 2005).

2. Morphology, immunoreactivity and connections of thalamic reticular neurons

The RE nucleus is a derivative of the ventral thalamus (Jones, 1985) and is entirely composed of GABAergic cells (Houser et al., 1980). It is a relatively thin sheet of neurons that surrounds the anterior, lateral and to some extent ventral surfaces of the dorsal thalamus. Because of its anatomical position, the RE nucleus is traversed by virtually all axons connecting the dorsal thalamus with the neocortex, giving the nucleus its reticulated appearance and name. RE neurons have long dendrites (Fig. 2), whose secondary and tertiary branches possess vesicle-containing appendages that form synapses on the dendrites of neurons in the same nucleus. The presynaptic dendritic appendages are common in cats (Deschênes et al., 1985; Yen et al., 1985), present but rare in monkeys (Williamson et al., 1993), and reportedly absent in rats (Ohara and Lieberman, 1985).

The cells of the RE nucleus have soma diameters of 20–50 μm, and are generally ovoid, with relatively long dendritic branches emerging from the poles of the soma (Fig. 2). Even though RE neurons seem to be relatively homogeneous from the morphological point of view, there is evidence for functional differences. As yet, there are no morphological correlates of the two neuronal populations of the RE nucleus, one of which generates low-threshold spikes (LTSs) and is able to switch from tonic to burst firing, the other apparently lacking the low-threshold Ca^{2+} conductance and firing only tonically (Contreras et al., 1992). The latter group is similar to the overwhelming majority of neurons in the ventral lateral geniculate nucleus (Crunelli et al., 1987) that share a common embryological origin with the RE nucleus and similarly do not project to cortex (Jones, 1985). Another example of functional, but not related to morphological, diversity is the presence of a subgroup of RE neurons which display intrinsic membrane bistability, likely due to the functional expression of a persistent Na^+ current, $I_{Na(p)}$ (Fuentealba et al., 2005) (see details in Section 3.1).

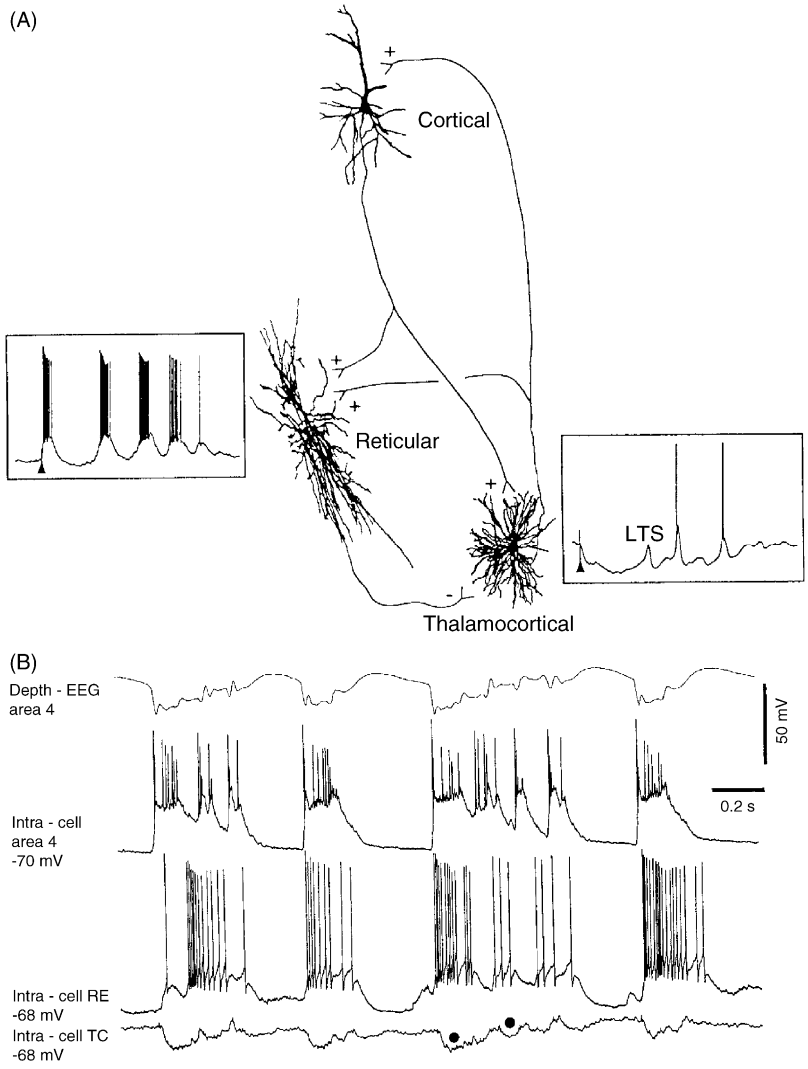

Fig. 1. Relations between corticothalamic, thalamic reticular (RE) and thalamocortical (TC) neurons. (A) Three neurons (cortical, RE and TC) were intracellularly recorded and stained in cats. Signs of excitation and inhibition are indicated by plus and minus. For the sake of simplicity, local-circuit 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 a depolarizing envelope (membrane potential, −68 mV). The TC neuron responded to cortical stimulation (arrowhead) with a biphasic, $GABA_{A–B}$-mediated IPSP, leading to a low-threshold spike (LTS) and a sequence of hyperpolarizing spindle waves (membrane potential, −70 mV). (B) Relations between cortical (area 4), RE and TC neurons of cat during spontaneously occurring, cortically generated seizure with polyspike-wave (PSW) complexes at 2 Hz. Note IPSPs in TC neuron (filled circles) in close time relation with spike-bursts fired by RE neuron, driven from cortex. Modified from Steriade et al. (1993), Contreras and Steriade (1996), Lytton et al. (1997) and Steriade (2000).

The axons of cat RE neurons are relatively thin (around 1.5 μm), but myelinated when passing into the underlying dorsal thalamus. Within the RE nucleus, they give off two or three short unmyelinated collaterals which end in bouton terminals close to the cell body of origin. These boutons contain flattened synaptic vesicles and end in symmetrical synapses observed under electronic microscopy (Yen et al., 1985), but in appropriate sectors of the RE nucleus some of these probably also arise from axons of pallidal and basal forebrain origin (Asanuma, 1994; Asanuma and Porter, 1990). Although some authors have denied the presence of intranuclear collaterals in the rat RE nucleus (Pinault et al., 1995), such collaterals have been found in numerous other studies on both cats and rats (Steriade and Deschênes, 1984; Yen et al., 1985; Spreafico et al., 1988; Lubke, 1993). On entering the dorsal thalamus, the axons of RE neurons ramify mainly in the nucleus related to the sector of the RE nucleus in which the parent cell lies, though collaterals are also distributed in adjacent or even more distant nuclei.

Besides their immunoreactivity to GABA, other substances expressed in RE neurons are parvalbumin, the CAT301 antigen, and certain neuropeptides such as somatostatin and neuropeptide Y (Oertel et al., 1983; Molinari et al., 1987; Morris, 1989).

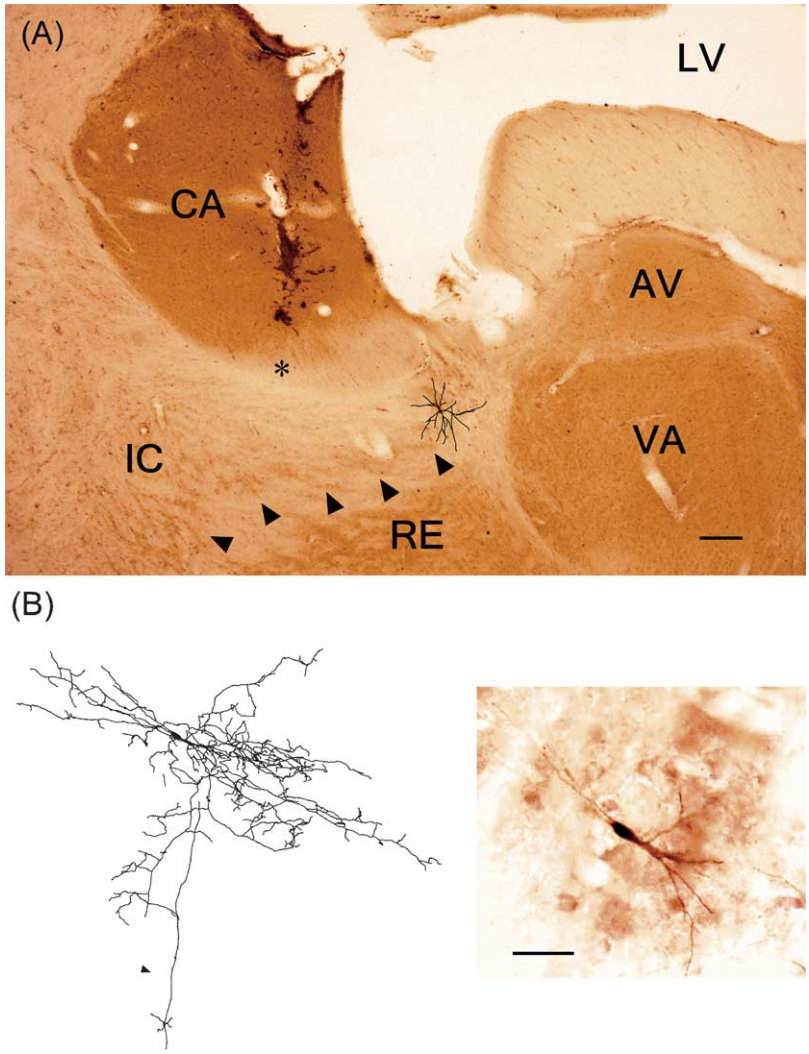

Fig. 2. Morphology of thalamic reticular (RE) neurons. (A) Microphotograph of a section (80 μm thick) where an intracellularly stained RE neuron of cat (Neurobiotin) was recovered. Frontal section. Reconstruction shows the relative position of the neuron. Arrowheads point to the rostrolateral sector of the RE nucleus. Asterisk marks the stimulating electrode in the internal capsule (IC). Abbreviations: AV, anteroventral nucleus; CA, caudate nucleus; IC, internal capsule; LV, lateral ventricle; RE, reticular nucleus; VA, ventroanterior nucleus. Scale bar: 500 μm. (B) Another intracellularly stained cat RE neuron located in the rostrolateral sector of the nucleus. Photograph (right) and reconstruction (left). Arrowhead indicates the axon to the dorsal thalamus. Calibration bar within the photograph = 0.1 mm for RE neuron in the photograph and 0.15 mm for the reconstructed neuron. Modified from Fuentealba et al. (2004b).

2.1. Intrathalamic circuits and corticothalamic projections

The excitatory postsynaptic potential (EPSP) elicited in a RE neuron by stimulating the motor thalamic nucleus (Fig. 3) exemplifies the direct projection from TC to RE neurons, and the antidromic invasion of the motor cortical neuron in this figure shows the return projection from the related cortical area to the dorsal thalamus. The synaptic activation of the RE neuron by thalamic stimulation could also be due to axon reflex excitation of this neuron following antidromic activation of the corticothalamic axon. The dual intracellular recording from cortex and RE nucleus in Fig. 3 also demonstrates that spindle oscillations invariably started in the RE nucleus.

The GABAergic RE neurons exert influences on the two other thalamic cell classes: TC neurons and local-circuit GABAergic cells. The latter constitute about 25% of the total neuronal population in all dorsal thalamic nuclei of cats and primates (Steriade et al., 1997). With the exception of the lateral geniculate nucleus, local inhibitory neurons are absent in dorsal thalamic nuclei of rats, a species on which most in vitro studies are conducted. However, although the RE–TC connection is the only projection that is generally considered in simplistic descriptions of thalamic circuitry and only about 10% of thalamic RE neurons project to local inhibitory interneurons (Liu et al., 1995), the synaptic weight of this projection is unknown and it may produce significant effects on the ultimate targets, TC neurons. Indeed, the projection from RE neurons to local interneurons may eventually lead to the disinhibition of TC cells neurons. This has been demonstrated by increased incidence of inhibitory postsynaptic potentials (IPSPs) in TC neurons

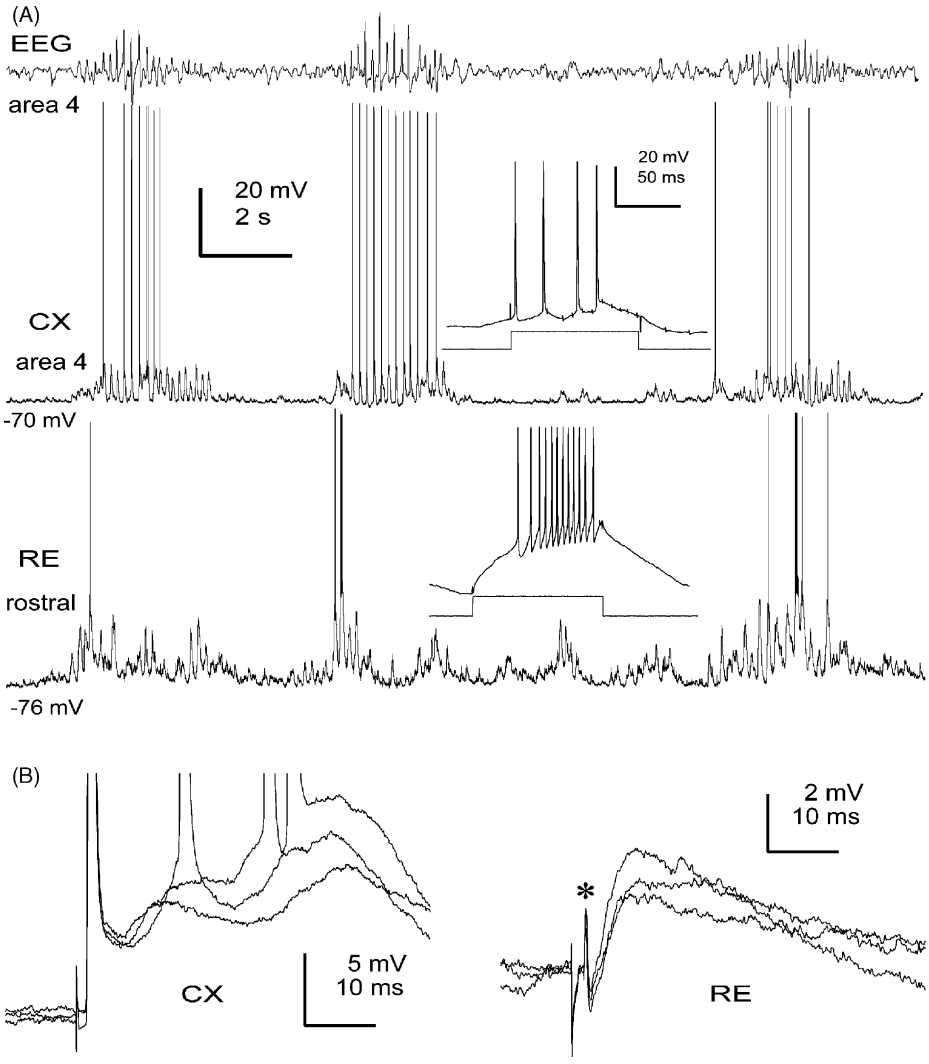

Fig. 3. Spindle oscillations in the cortex and thalamic RE nucleus. Cat under barbiturate anesthesia. (A) Simultaneous intracellular recordings from a cortical neuron (CX, area 4) and a thalamic RE neuron in the rostral part of the nucleus. Note synchronization of intracellular and cortical EEG activities (area 4); however, spindles invariably started in the RE nucleus. Note also the very rich synaptic background activity in the RE neuron, compared to the cortical one. Intracellular injection of positive current pulses identified both neurons. The cortical cell fired thick action potentials and displayed low frequency discharge, whereas the RE neuron generated a powerful low-threshold calcium spike crowned by thin, fast action potentials. (B) Electrical stimulation of thalamic ventrolateral (VL) nucleus identified the cortical cell as corticothalamic. Note antidromic action potential, followed by synaptic activation. VL stimulation also generated short, fixed latency EPSP in the RE neuron, preceded by a small artifact (asterisk) due to the capacitive coupling between both intracellular recordings. Note that the latency of the artifact in the RE neuron corresponds to the peak of the antidromic action potential in the cortical pyramidal cell (1.4 ms). Therefore, both neurons belonged to the same functional TC circuit, involving VL, RE and cortical area 4. Unpublished data by P. Fuentealba and M. Steriade.

after excitotoxic lesions of RE perikarya, as if local interneurons were released from the inhibition exerted by RE neurons (Steriade et al., 1985). It was proposed that the connection between the two types of inhibitory cells, RE and local-circuit interneurons, subserves processes for focusing attention to relevant signals (Steriade, 1999). Fig. 4 illustrates this hypothesis. The upper TC cell (Th-cx) in the figure receives prevalent excitation from the afferent fiber (Aff.) while the bottom Th-cx cells receives less collaterals from the Aff. axon. The RE neurons that are directly connected to the top Th-cx neuron (the top RE neuron is part of this pool) are activated from Aff. through collaterals of Th-cx cells and contribute to further enhancement of relevant activity by inhibiting the pool of local-circuit (L-circ) elements (the top L-circ neuron is part of this pool). Simultaneously, the activity in adjacent RE areas (bottom RE neuron) is suppressed by axonal collateralization and dendro-dendritic synapses within the RE nucleus. The consequence would be the released activity of target L-circ neurons (bottom L-circ cell) and inhibition of weakly excited TC neurons (bottom Th-cx neurons) in areas adjacent to the active focus. The full functional consequence of this GABAergic-to-GABAergic (RE to local-circuit) connection remains to be investigated.

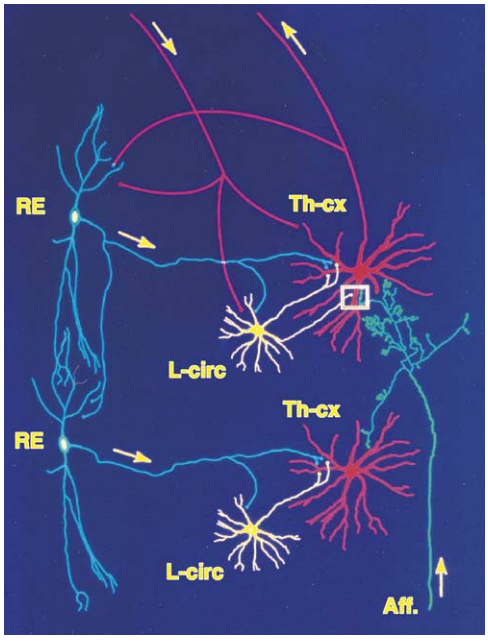

Fig. 4. Relations between GABAergic thalamic reticular (RE) and local-circuit (L-circ) neurons, and their effects on thalamocortical (Th-cx) neurons. See text for explanation of circuitry and possible functional consequences. This hypothesis derived from a study on the activity of RE neurons during the natural waking-sleep cycle (Steriade et al., 1986). The circuit was proposed in Steriade (1991) and was redrawn by E.G. Jones. Modified from Steriade (1999).

The major sources of afferent inputs to the RE nucleus are the collaterals of corticothalamic axons (Liu and Jones, 1999). The functional predominance of cortical inputs, over those from TC neurons, was demonstrated in a study showing that the numbers of glutamate receptor subunits GluR4 are 3.7 times higher at corticothalamic synapses in RE neurons, compared to TC neurons, and that the mean peak amplitude of corticothalamic excitatory postsynaptic currents (EPSCs) is about 2.5 higher in RE, than in TC, neurons (Golshani et al., 2001). This explains why corticothalamic pathways, which are glutamatergic and excitatory in nature, may exert opposite effects on RE and TC neurons during the burst mode of firing. Electrical stimuli or naturally occurring synchronous volleys in corticofugal axons excite RE neurons and produce rhythmic spike-bursts, whereas they induce biphasic ($GABA_{A-B}$) IPSPs in TC cells, due to the prior excitation of RE neurons (see above, Fig. 1A).

2.2. Neuromodulatory pathways

Afferent inputs from neuromodulatory systems to the RE nucleus arise in the brainstem and basal forebrain. The major sources of brainstem reticular inputs arise from mesopontine cholinergic nuclei (Paré et al., 1988; Raczkowski and Fitzpatrick, 1989) and monoaminergic, locus coeruleus and dorsal raphe nuclei (Morrison and Foote, 1986). The monoamine projection is of importance because it slightly depolarizes RE neurons and thus explains, at least in part, the differences between the in vivo results, which reported the presence of spindle oscillations in RE neuronal networks, and the failure of recording spindles in slices maintained in vitro (see Section 4.1). Basal forebrain afferents arise in cholinergic cells (less than 50% of the retrogradely labeled neurons) and GABAergic cells (Steriade et al., 1987b; Parent et al., 1988; Cornwall et al., 1990; Asanuma, 1997). The afferents from the pretectum mainly arise in the GABAergic neurons of the optic tract nucleus (Cucchiaro et al., 1993).

3. Electrophysiology of thalamic reticular neurons

3.1. Intrinsic properties and their modulation by synaptic inputs

There are some similarities between RE and TC neurons in their bursting and tonic discharge modes during different states of vigilance (Steriade et al., 1990). The bursting mode occurs during slow-wave sleep, while tonic discharge is detected during brain-activated states of waking and rapid-eye-movement sleep (Steriade et al., 1986). The two firing modes of thalamic neurons depend on their membrane potential (Llinás, 1988). At relatively depolarized membrane potentials (positive to −65 mV), intracellular injection of a depolarizing current pulse results in a train of single action potentials, whereas intracellular injection of the same current pulse at hyperpolarized membrane potentials results in the generation of a high-frequency (300–500 Hz) burst of action potentials in most RE neurons (Contreras et al., 1992, 1993; Bal and McCormick, 1993). As in TC neurons (Llinás, 1988), such high-frequency bursts are generated in RE neurons by activation of the low-threshold Ca^{2+} current, T-current (Huguenard, 1996).

The bursts of action potentials generated in RE neurons are dissimilar to those of TC cells, the main differences being their duration and internal structure. Quantitative analyses of spike-bursts fired by thalamic neurons during natural slow-wave sleep (Domich et al., 1986; Steriade et al., 1986) showed that bursts in TC neurons (5–20 ms in duration) display 3–5 action potentials, whereas more than 90% of bursts in RE neurons are longer than 50 ms and contain 5–8 or more spikes. The intrinsic burst structure is also different in these two thalamic cell classes. While spike-bursts in TC neurons show a progressive increase in interspike interval duration, RE neurons display a decrease followed by increase in interval duration, called accelerando–decelerando pattern (Domich et al., 1986; Steriade et al., 1986) that was ascribed to the dendritic location of T-currents in RE neurons (Destexhe et al., 1996). The secondary depolarizing component of cortically evoked EPSPs in RE neurons (Contreras et al., 1993) may also shape their spike-bursts. This component occurs as an all-or-none event at about 5 ms after the peak of the initial

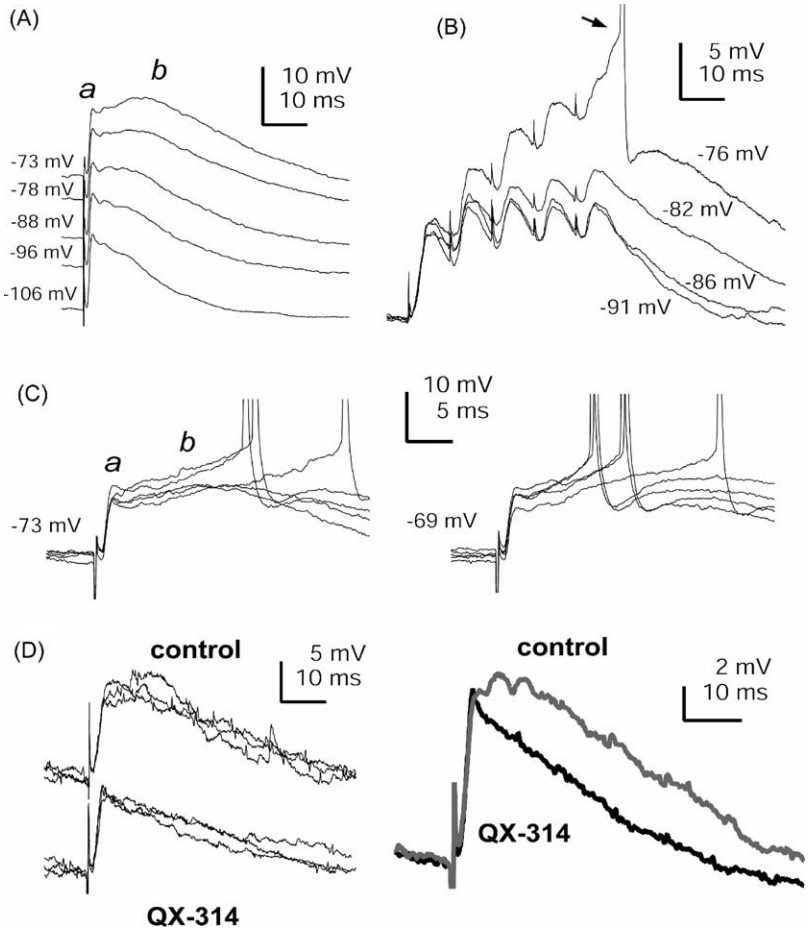

Fig. 5. The secondary depolarizing component of cortically evoked EPSPs controls the output of thalamic RE neurons. Cat under barbiturate anesthesia. (A–D), Four different RE neurons. (A) Averages ($n = 20$) of cortically evoked EPSPs. Two components in the response: an early, constant component (a) and a late, voltage-dependent component (b). (B) The secondary component of EPSPs affects the temporal summation of inputs in a voltage-dependent fashion (5 stimuli at 100 Hz). Arrowhead indicates the threshold for spike generation. (C) The action potential and its precise timing were also modulated by the secondary component. (D) Left, superimposed evoked EPSPs ($n = 3$) recorded at resting V_m (−78 mV) at the beginning (top) and after 7 min (bottom) of recording with QX-314 (50 mM) in the pipette. Right, average ($n = 10$) of evoked EPSPs showing the effect of QX-314 on the late component of the response (V_m, −76 mV). Modified from Fuentealba et al. (2004a).

EPSP and is voltage-dependent, being most prominent between −70 and −85 mV and greatly reduced or absent at more hyperpolarized levels (Fig. 5A). The secondary depolarizing component is sensitive to QX-314 in the recording micropipette (Fig. 5D), suggesting that $I_{Na(p)}$ contributes, together with the dendritic activation of T-currents, to this component of cortically evoked EPSPs (Fuentealba et al., 2004a). The secondary EPSP affects the integrative properties of RE neurons, including their spiking output and temporal summation of incoming cortical inputs. Thus, the early component of EPSP generates stereotyped spikes at short and fixed latencies, at relatively depolarized values, while the secondary depolarizing component triggers spikes with widely variable latencies at more hyperpolarized values, around −70 mV (Fig. 5B and C).

The accelerando–decelerando pattern of spike-bursts in RE neurons is often followed by a prolonged tonic tail of single, tonic spikes. This tail was originally described using extracellular recordings in naturally sleeping animals (Domich et al., 1986; Steriade et al., 1986) and was also recently reported with intracellular in vivo recordings (Fuentealba et al., 2005). The presence of this long tail of tonic spikes is related to the expression of membrane bistability in a subpopulation (20%) of RE neurons, and seems to be relevant not only for the intrinsic activity of RE neurons but also in sculpting the patterns of spindle oscillation in the thalamus (Fig. 6). Actually, intracellular recordings of TC neurons show the existence of at least two different spindle patterns. In the first, TC neurons exhibit cyclic, powerful sequences of waxing and waning IPSPs originated from the RE nucleus (cell 2 in Fig. 6). At the end of IPSPs' cycles, a strong rebound is generated and crowned by action potentials. The second pattern is much more irregular; it does not show clear waxing and waning IPSPs or rebound discharge at the end

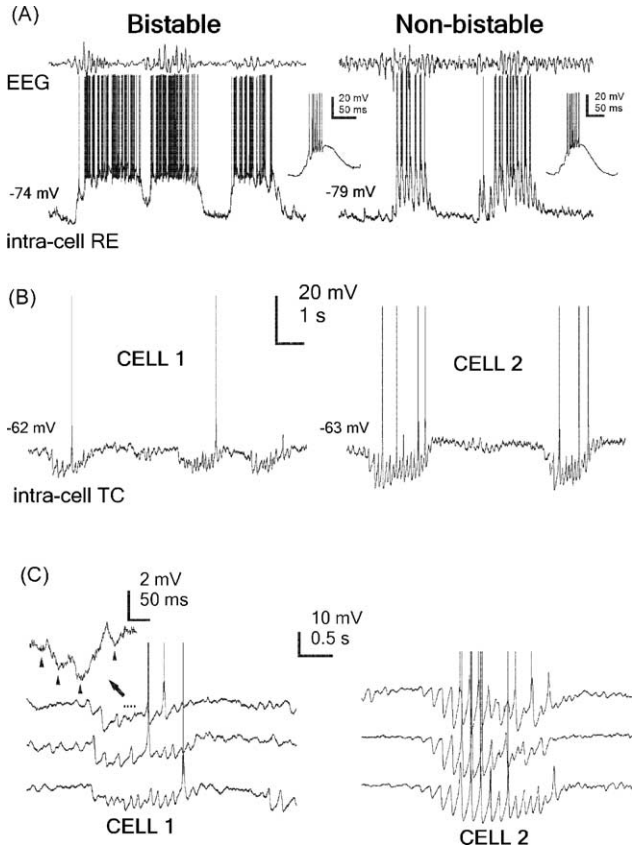

Fig. 6. Membrane bistability in thalamic RE neurons shapes spindle oscillations in TC neurons. Cat under barbiturate anesthesia. (A) Cortical EEG and intracellular recordings from two RE neurons. Typical low-threshold spike-bursts of each of these RE cells are expanded in insets. Calibration is same for both RE and TC neurons in (B). Bistable RE neuron displayed sustained depolarizations throughout spindle waves. Non-bistable RE neuron fired spike-bursts, separated by phasic hyperpolarizations, during spindling. (B) Different spindling patterns in TC cells reflect the two firing patterns in the above depicted RE neurons. Intracellular recordings of two TC neurons (ventrolateral, VL, nucleus) during spindle activity. (C) Three different spindle sequences for each of the above TC cells. Note highly regular activity and early rebound bursting in cell 2. Inset in cell 1 shows three IPSPs (arrows) at higher frequency (~20 Hz) than the usual frequency range of spindles (10 Hz). See also text. Modified from Fuentealba et al. (2005).

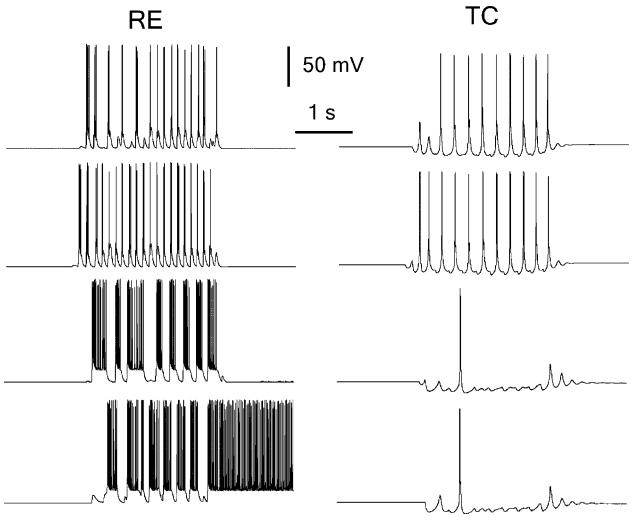

Fig. 7. Membrane bistability in thalamic RE neurons may contribute to the termination of thalamic oscillations. Computational models predict that membrane bistability of RE neurons (see experimental data in previous Fig. 6) modulates patterns of spindle oscillations in TC neurons. Shown are four RE and four TC neurons from a one-dimensional simulated thalamic network of connected cells (26 RE and 26 TC) during active periods of thalamic oscillations. The different patterns of activity in RE neurons had a differential effect on target thalamic neurons, depending on the connectivity in the reciprocal network. The two RE neurons in the top are classic (non-bistable) ones, while the two at the bottom were modeled with the inclusion of a persistent Na^+ current ($I_{Na(p)}$), which results in the expression of membrane bistability. Note that TC cells receive projections from multiple RE neurons; therefore, the final effect on spindling pattern was a combination between those multiple inhibitory inputs. Accordingly, TC neurons receiving preferentially projections from non-bistable RE neurons displayed robust, regular oscillations, with rebound spike-bursts in most cases (two upper traces). Conversely, TC cells receiving inputs mainly from bistable RE neurons showed irregular rhythms, associated with very low rebound discharges (two lower traces). See similar patterns in the previous figure with experimental data. In fact, the spatio-temporal pattern of activity in the modeled thalamic network showed some TC neurons that were hyperpolarized and did not fire during the active periods of this type of thalamic oscillations (not shown). This suggests a possible contribution to the termination of spindles. Modified from Fuentealba et al. (2005).

of every cycle (cell 1 in Fig. 6). Modeling studies (Fuentealba et al., 2005) showed that the discharge patterns in TC neurons produced by intrinsic bistability in RE neurons could contribute to generate less and less spikes in rebounds of TC cells, therefore contributing to terminate spindle waves in the thalamus (Fig. 7). This possible way of spindle termination may act together to the two other proposed mechanisms. One of these factors is the Ca^{2+}-dependent increased activation of the hyperpolarization-activated cation current, I_H (Bal and McCormick, 1996). This would result in a relative refractory period during which the propensity to generate synchronized oscillations is markedly reduced. Another mechanism for the termination of spindles would depend on the desynchronization of thalamic oscillatory activity, due to LTS' generation with different delays from the onset of IPSP and/or to strong depolarizing cortical inputs onto thalamic neurons, which would prevent the generation of LTSs and thus will lead to the spindle termination (Timofeev et al., 2001).

The graded nature of LTSs in RE neurons was characterized in vivo (Contreras et al., 1993) and depends on the distal dendritic localization of T-channels coupled with the constant synaptic bombardment of dendritic arbors by network activity. Intracellular recordings in RE neurons in vivo revealed small-amplitude (3–7 mV) potentials that are different from EPSPs and probably represent regenerative events originated in the distal dendritic arbor. These presumed dendritic spikes could be triggered by intracellular current injection, by synaptic activation of excitatory inputs or by the depolarizing waves of spindle sequences (Contreras et al., 1993). They also occurred spontaneously, as single events or bursts (400 Hz). The dendritic spikes in RE neurons trigger LTSs and produce somatic depolarization as well as depolarizing potentials in more distal dendrites.

The spike-bursts of RE neurons are significantly prolonged during the transition from normal sleep behavior to epileptic seizures (Steriade and Contreras, 1995).

The ongoing synaptic background activity powerfully modulates membrane properties of RE neurons, including the LTSs. This was studied by means of in vivo intracellular recordings during periods of intense synaptic activity, represented by spindle waves (Fuentealba and Steriade, 2005). At resting conditions, V_m distribution of RE neurons was dominated by silent states, corresponding to single-peak histograms at hyperpolarized levels (around −75 mV). RE neurons showed low-pass filter properties, strongly dumping frequencies higher than 10 Hz, the main component of spindle waves. During spindles, the massive activation of T-currents generated powerful LTSs which dramatically changed V_m of cells (by 10–20 mV) and increased membrane fluctuations in one order of magnitude, from 1–3 mV to 10 mV (Fig. 8A and B). The generation of LTSs reduced the apparent input resistance up to 80% for 20–30 ms, in a cyclic way (Fig. 8C). These changes in basic membrane properties proved to be functionally significant for RE neurons, since both synaptic and intrinsic responsiveness were enhanced during active network states. Thus, synaptic responses tested by stimulating corticothalamic pathways showed increased spiking responses; the same result was found for intrinsic responses tested by positive and negative current pulses, as well as sinusoidal wave currents (Fuentealba and Steriade, 2005).

In sum, the voltage-dependent dendritic channel distributions in RE neurons provide them with properties for integration of cortical inputs that are the most powerful among afferent excitatory signals (Golshani et al., 2001). Compared with the effects these inputs exert on TC neurons, at which level dendritic currents generate high-frequency rhythms (Pedroarena and Llinás, 1997) that define brain alertness, the parallel activation of RE-cells' dendrites by synchronized cortical volleys produces low-frequency oscillations (Contreras and Steriade, 1996) that characterize the disconnected state of slow-wave sleep.

3.2. Neuronal substrates of synchronization within the reticular nucleus

The two ways through which RE may synchronize their rhythmic activities within the nucleus are GABAergic synapses and the more recently revealed electrical coupling.

Initially, the presence of oscillations within the in vivo deafferented RE nucleus was ascribed to an avalanche of IPSP-rebound sequences at 10–15 Hz, through dendro-dendritic GABAergic synapses, which could start in any point of the RE neuronal network and spread to adjacent and distant neurons (Steriade et al., 1987a). However, the belief from some in vitro studies, which did not focus on spindles but on "epileptiform" activity, was that reciprocal inhibitory connections among RE neurons act as desynchronizers, thus preventing thalamocortical synchrony (Huntsman et al., 1999; Huntsman and Huguenard, 2000). Nonetheless, a

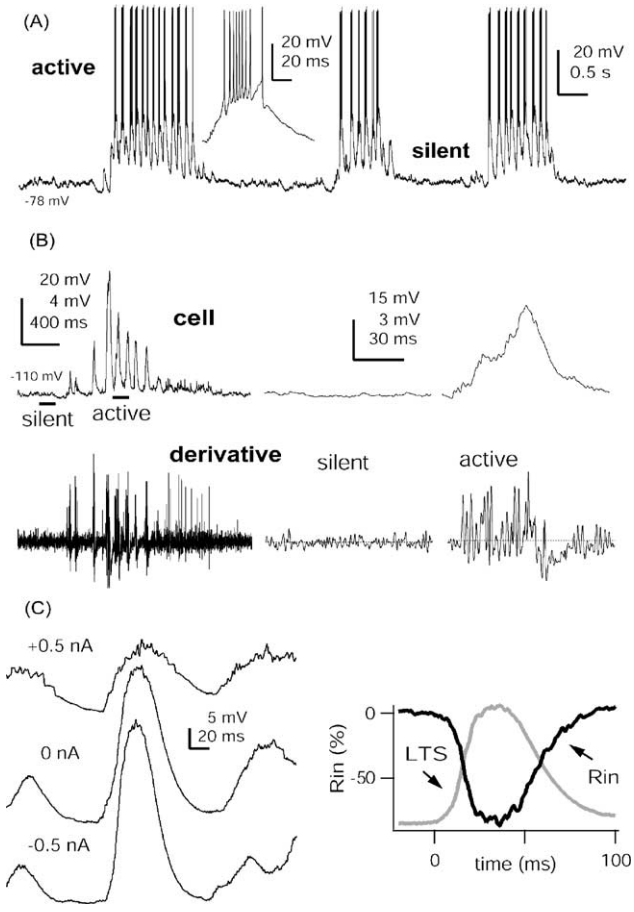

Fig. 8. Spindle oscillations modulate membrane properties of RE neurons. Cat under barbiturate anesthesia. (A) Neuron recorded at rest in the rostral pole of the RE nucleus. Note alternate states of spike-bursts activity (active) and quiescence (silent), characteristic of spindle waves. Inset, typical burst of action potentials displaying accelerando–decelerando pattern. (B) Left, period of spindle waves in the same neuron, but hyperpolarized by negative current injection (−1 nA) to avoid action potential discharge. Below, derivative of the previous period. Silent and active indicate episodes expanded in middle and right panels, respectively. Note the higher level of background activity during active states, constituted not only by slow potentials as LTSs (cell), but also small-amplitude, short-duration events (derivative). (C) Left, averages (n = 10) of LTSs occurring during spindle waves recorded at different levels of steady current injection. Right, time-course of changes in apparent input resistance during LTSs. Note the input resistance to decrease quickly up to 80%, only to slowly recover after every single LTS. Modified from Fuentealba and Steriade (2005).

study from the same laboratory acknowledged that the slow time constant of evoked IPSC decay in RE neurons is consistent with studies of spindle synchrony in an interconnected network of inhibitory cells (Zhang et al., 1997). Actually, computational studies using minimal or more realistic ionic models of isolated networks of GABAergic RE neurons (Wang and Rinzel, 1993; Destexhe et al., 1994a; Golomb et al., 1994) have corroborated our hypothesis that mutual GABAergic inhibition between RE neurons can synchronize them into spindle-like oscillations. In modeling studies, synchronous oscillations of "cluster" states were similar to those described in the in vivo study in

which spindles were only found in distinct foci of the RE nucleus, supposed to contain dendritic bundles (Steriade et al., 1987a). Subsequent experimental studies demonstrated that, at the relatively hyperpolarized levels of slow-wave sleep, the IPSPs resulting from contacts among RE neurons can be reversed and computational work revealed that $GABA_A$-mediated depolarization can generate persistent spatio-temporal patterns of spindles in the isolated RE nucleus (Bazhenov et al., 1999).

Another, non-exclusive mechanism of spindle synchronization within the RE nucleus is the electrical coupling by gap junctions. The first evidence came from an in vitro work (Landisman et al., 2002) that, surprisingly, did not find evidence for chemical GABAergic synapses within the nucleus, though this is commonly reported by all morphological and electrophysiological studies. The electrical coupling in RE nucleus depends on the expression of a connexin protein, Cx 36, and its features are similar to those of most electrical synapses that have been studied in vertebrate nervous systems. Further in vitro (Long et al., 2004) and in vivo (Fuentealba et al., 2004b) experiments also showed that many RE neurons are interconnected by electrical synapses. In our study, spontaneously occurring spikelets, which are characteristic of central neurons that are coupled electrotonically via gap junctions, occurred spontaneously during spindles and during interspindle lulls. Spikeles are much smaller than action potentials (common amplitude ratio, 1:50). They are significantly different from EPSPs (Fig. 9) and also distinct from fast prepotentials (FPPs) that are presumably dendritic spikes generated synaptically. That spikelets and EPSPs were different events resulted from two major features. Firstly, spikelets had much faster rising and decaying phases than EPSPs. Secondly, spikelets were unable to elicit full action potentials, even during states of membrane depolarization close to firing threshold, whereas EPSPs led to cell firing at the same level of depolarization (Fig. 9B). As to FPPs, their amplitudes were much greater than those of spikelets, and their time-course was also different. In contrast to spikelets, FPPs were mainly present during periods of membrane depolarization (Fuentealba et al., 2004b). Spikelets were strongly reduced by halothane, a blocker of gap junctions (Fig. 10).

The relatively strong filtering properties of electrical connections between RE neurons exclude fast events as spikes, but favor the synchronization of low frequency events, such as LTSs and slower oscillations. This means that, together with chemical GABAergic synapses, electrical coupling might synchronize oscillations in the range of spindles, which are mediated by LTSs (Fig. 11).

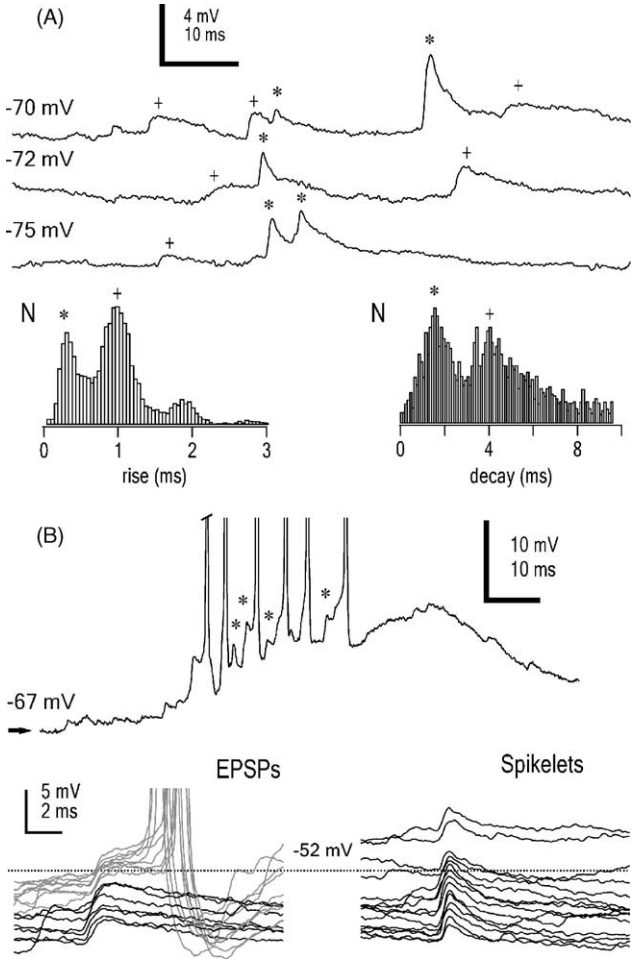

Fig. 9. Spikelets and EPSPs are different types of depolarizing events. (A) Cat under barbiturate anesthesia. Top three traces, from the same RE neuron, show two types of depolarizations: spikelets (*) and EPSPs (+). Below, two histograms show the distribution of the rising and decaying phases (left and right, respectively) in the two types of events. (B) Another neuron, in cat under ketamine–xylazine anesthesia. Spikelets (*) are present during the firing of RE cell (spikes truncated). Note different rising phases in spikelets. Some EPSPs gave rise to action potentials. Below, superimposed traces from the same neuron showing EPSPs and spikelets. From Fuentealba et al. (2004b).

4. Generation of spindles in the thalamic reticular nucleus

We will first briefly present the initial data, demonstrating the presence of spindle rhythmicity in the in vivo deafferented RE nucleus, and the different factors that may account for the failure of recording spindles in isolated RE slices maintained in vitro. Next, we will present recent data from in vivo and in computo studies providing new arguments for the generation and synchronization of spindles within the RE nucleus, as well as the wider synchronization of this oscillation in TC and corticothalamic systems.

Spindles are sequences of waxing-and-waning waves at frequencies of 7–15 Hz, which recur periodically with a frequency of 0.2–0.5 Hz. Although TC neurons are inhibited during spindles and are therefore unable to transfer incoming signals to the cerebral cortex, thus disconnecting the brain from the external world, spindles are operational in

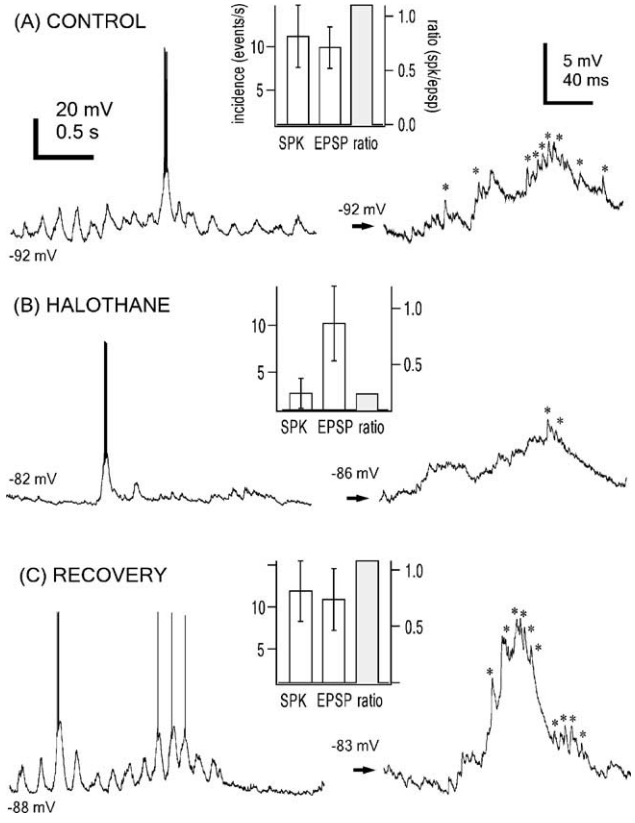

Fig. 10. Spikelets are strongly reduced or virtually abolished by halothane. Cat under barbiturate anesthesia. Left column, different epochs before (A), during halothane administration (B), and recovery of initial state after halothane (C). Right column, expanded periods from neurons depicted in the left column. Insets: incidence of spikelets (SPK) and EPSPs (left ordinate), and their ratio during a 5-min-period of recording (right ordinate), in each of the three states. From Fuentealba et al. (2004b).

producing synaptic plasticity within the thalamus and neocortex, which may underlie consolidation of memory traces acquired during the state of waking (Steriade, 2003; Steriade and Timofeev, 2003).

4.1. Presence of spindles in the in vivo deafferented reticular nucleus and factors accounting for absence of spindles in slices of reticular nucleus

The in vivo study that initially reported the presence of spindles in the deafferented rostral pole of the RE nucleus performed transections that separated the RE nucleus from cortex and the remaining thalamus, but left intact an island, medio-ventrally, through which some projections from brainstem monoamine-containing neurons might have been intact (see Fig. 2A and C, in Steriade et al., 1987a). The disconnection of RE nucleus from the dorsal thalamus, which was later hypothesized to contribute to spindles' initiation (von Krosigk et al., 1993), was complete, as verified histologically. As to neocortex, earlier experiments have shown that it is not necessary for the generation of thalamic spindles (Morison and Bassett, 1945). The island medio-ventral to the rostral pole of the RE nucleus, through which brainstem monoaminergic could survive, is significant because these projections exert a depolarizing action on RE neurons (McCormick, 1992; Steriade et al., 1997), a factor that favors spindle generation within the RE nucleus (see below) since the resting membrane potential of RE neurons is slightly more depolarized in vivo than in vitro. Nonetheless, all computational studies on this topic agreed that spindles occur even in completely isolated networks of GABAergic neurons (see below). In the in vivo preparation (Steriade et al., 1987a), spindle oscillation was observed in circumscribed territories of the RE nucleus and contrasted with the absence of spindles in the remaining thalamus and cortex. Along the same microelectrode track, more dorsally or ventrally explored areas did not display spindling, which led to the proposal that spindle activity was prevalent in those RE areas in which highly concentrated dendritic bundles are present (Steriade et al., 1987a). In vitro experiments, however, failed to record spindles in the isolated visual (perigeniculate) sector of the RE nucleus (von Krosigk et al., 1993). Some factors accounting for this failure are as follows.

The cut for slices maintained in vitro leads to a less intact collection of RE neurons (see note 13 in Steriade et al., 1993) by partially mutilating the long dendrites of these neurons. The role of dendrodendritic inhibitory contacts among RE neurons in spindle generation has been initially hypothesized (Steriade et al., 1987a) and the dendritic location of LTSs in RE neurons was demonstrated (Huguenard and Prince, 1992) together with the presence of spike-bursts in presumed dendritic recordings from RE neurons (Contreras et al., 1993). That the dendrites of RE neurons are implicated in the bursting properties leading to spindles was demonstrated in an in vivo, in vitro and in computo study (Destexhe et al., 1996) showing that, in contrast to RE cells with intact dendritic arborizations in which there is a high density of low-threshold transient Ca^{2+} currents, RE cells in which most of the dendritic arborizations were removed have a much lower density of I_{Ts}. These data support the initial hypothesis postulating that, in the deafferented RE nucleus, the de-inactivation of the low-threshold Ca^{2+} conductance in dendrites gives rise to spike-bursts and hyperpolarization of postsynaptic dendrites in synaptically coupled neurons, eventually leading to an avalanche of IPSP-rebound sequences at ~10–15 Hz, distributed throughout the RE nucleus (Steriade et al., 1987a).

The idea that a collection of RE neurons more intact than that normally found in a thalamic slice may give rise to spindles is supported by modeling studies, based on intracellular recordings in vivo, showing that only transient oscillations could be obtained in a network smaller than 25×25 RE neurons, while larger, two-dimensional networks population produced oscillations with a frequency around 10 Hz, like spindles (Bazhenov et al., 2000). This difference emphasizes the requirement for numerous RE neurons in producing synchronized oscillations.

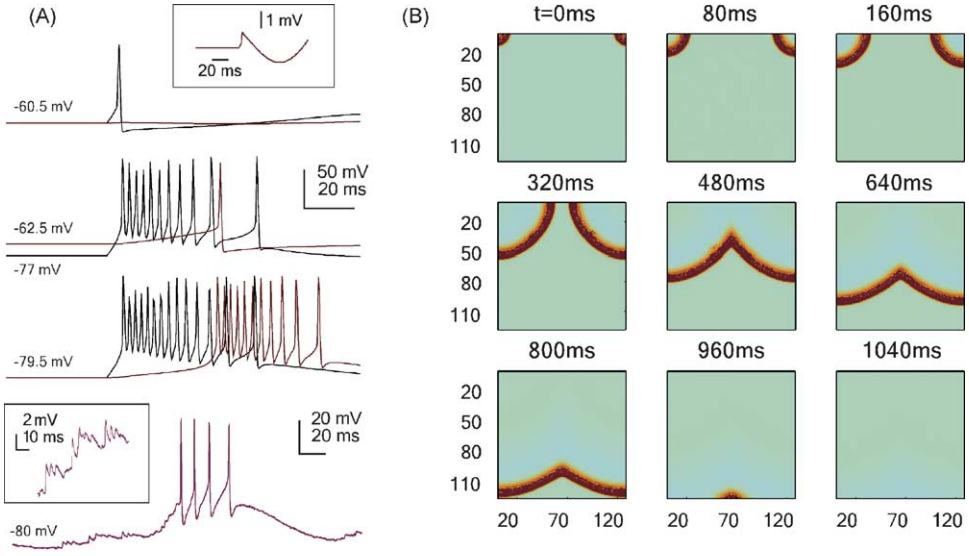

Fig. 11. Electrical synapses may spread and synchronize thalamic oscillations. (A) Model of a pair of reciprocally connected RE neurons. A spikelet (inset) was induced in the postsynaptic cell (red lines) by a single spike in the presynaptic neuron (black lines). Upon hyperpolarization of the presynaptic neuron (second trace), a burst of spikes can trigger a single spike in the postsynaptic neuron. When both cells are hyperpolarized (third trace), a burst in the presynaptic cell can induce a delayed spike-burst in the postsynaptic cell. Bottom trace represents intracellular recording of RE neuron in vivo, showing the similarity with the prediction of the model. Inset, clusters of high-frequency spikelets preceding low-threshold spike. (B) Wave dynamics in two-dimensional network of RE neurons. Two stimuli were applied simultaneously at the comers of a two-dimensional 128 × 128 network of RE cells interconnected with gap junctions. Firing cells are shown in red, silent neurons indicated by blue. Note the propagation of the wave of activity, mediated by electrotonic contacts. From Fuentealba et al. (2004b).

Additionally, modulatory systems arising in the brainstem are absent in thalamic slices. The depolarization of RE neurons by monoamine-containing systems (see above) promotes the sensitivity of RE neurons to the IPSPs generated by intra-RE GABAergic connections, with the consequence of generating spontaneous oscillations within the frequency range of spindles (Destexhe et al., 1994b). In that simulation study, RE neurons, organized with dense proximal connectivity, were examined in a hyperpolarized state (−65 to −75 mV), similar to the in vitro condition when no monoaminergic synapses are activated, and in a more depolarized state (−60 to −70 mV) that would correspond to a weak monoaminergic activity. In the more depolarized condition, RE neurons exhibited spindle-like rhythmicity, whereas at more hyperpolarized levels the oscillatory behavior was absent. Thus, an adequate level of monoaminergic-induced depolarization may change the state of isolated RE neuronal networks, from silence to spindle oscillations. Surprisingly, no experimental study in vitro was conducted during the past decade to test this possibility.

Besides the depolarization induced by monoamine-containing neurons, cortical depolarizing inputs to the RE neuronal network may reinforce its intrinsic propensity to generate spindles. Earlier (Steriade et al., 1972) and more recent (Contreras and Steriade, 1996) studies have indeed demonstrated that the most efficient way to trigger spindles is to activate corticothalamic projections that reach the distal dendrites of RE neurons. This action is also exerted by stimulating the contralateral cortex, to activate callosal and corticothalamic projections, thus avoiding antidromic activation of TC axons and collateral activation of RE neurons (Steriade et al., 1972). The callosal-corticothalamic pathway has recently been confirmed through intracellular recordings (Cissé et al., 2003).

4.2. Recent data supporting the generation of spindles in reticular nucleus

Experiments in our laboratory have supported the idea that spindle oscillations are locally generated in the RE nucleus. Intracellular recordings of RE neurons performed in vivo showed that in 30% of cases spindle oscillations are preceded by a long-lasting hyperpolarization (Fig. 12). Corticothalamic volleys were also effective in generating such hyperpolarizations followed by spindles in RE neurons (Fuentealba et al., 2004c). A drop of up to 40% in the apparent input resistance was associated with these hyperpolarizing potentials, suggesting an active process rather than disfacilitation. Accordingly, the reversal potential was around -100 mV for both spontaneous and cortically elicited hyperpolarizations, consistent with the activation of slow K^+ conductances in these cells (Ulrich and Huguenard, 1996a,b). QX-314 in the recording pipettes decreased both the amplitude and incidence of prolonged hyperpolarizations, suggesting the participation of G-protein dependent K^+ currents in the generation of hyperpolarizations (Hille, 1992). Simultaneous extracellular and intracellular recordings in the RE nucleus demonstrated that RE neurons discharged during the hyperpolarizations and, thus, may be

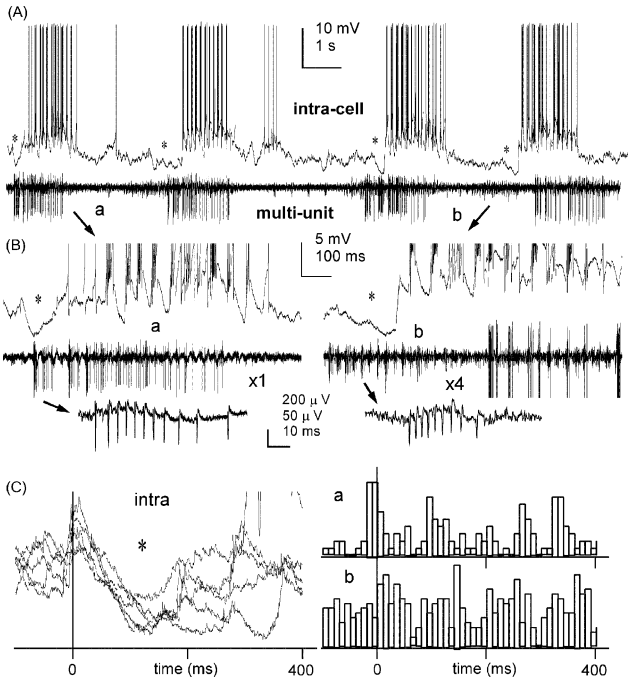

Fig. 12. Spindle oscillations can be locally generated in the thalamic RE nucleus. Distant RE neurons discharge during long-lasting hyperpolarizations preceding spindles. Cat under barbiturate anesthesia. (A) Simultaneous recording of intracellular (intra-cell) and extracellular (multi-unit) activities in the RE nucleus. Note the presence of two units in the extracellular recording (a and b). (B) Expanded traces from epochs in A, indicated by arrows. Left panel displays the first spindle sequence in A for both intra and extracellular recordings. Note discharge of one unit (a) during hyperpolarizations preceding spindles. Right panel depicts the last spindle sequence in (A). Note the second unit (b) firing during hyperpolarizations preceding spindles. Bottom traces depict typical accelerando–decelerando bursts for both units, identifying them as RE neurons. (C) Five superimposed traces showing long-lasting hyperpolarizations (left) and correlated discharge in both units for the same period (right). Modified from Fuentealba et al. (2004c).

implicated in their generation (Fig. 12). The prolonged hyperpolarizations preceding spindles may play a role in the transition from tonic to bursting firing of RE neurons within a range of membrane potential (−60 to −65 mV) at which they set favorable conditions for the generation of low-threshold spike-bursts that initiate spindle sequences. These data are further arguments for the generation of spindles within the thalamic RE nucleus. Additional evidence was provided by intracellular recordings and computational models showing that when RE neurons are hyperpolarized below the Cl^- reversal potential, synaptic excitation mediated by $GABA_A$ receptors can lead to low-threshold Ca^{2+} potentials crowned by Na^+ spikes (Bazhenov et al., 1999). This mechanism is able to produce propagating patterns of spike-burst activity, which also develop into self-sustained oscillations. This has also been supported by modeling studies showing that spiking-bursting activity in the RE nucleus might initiate sequences of spindle oscillations in thalamic networks (Bazhenov et al., 2000).

4.3. Intrathalamic and corticothalamic synchronization of spindles

During spindles, the rising phase leading to spike bursts in RE neurons is often preceded by high-frequency events of small amplitude, presumably EPSPs arising from spike-bursts from TC neurons (Mulle et al., 1986). These EPSPs are mainly mediated by non-*N*-methyl-D-aspartate (NMDA) receptors, since application of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptor antagonists results in block of spontaneous and evoked spindle waves (Bal et al., 1995) and NMDA components of cortically evoked responses in RE neurons are negligible (Gentet and Ulrich, 2004).

The synchronization of spindles over widespread thalamic and cortical territories is different in vitro and in vivo. Thus, in contrast to the nearly simultaneous spindle sequences seen in the thalamus and cerebral cortex in vivo, in acutely prepared animals as well as during natural slow-wave sleep in cats and humans (Contreras et al., 1996, 1997), spindles propagate along the dorso-ventral axis of the lateral geniculate nucleus in slices from the visual thalamus of ferrets, maintained in vitro (Kim et al., 1995). We hypothesized that the contrast between the simultaneity of spindle sequences in the intact brain and spindle propagation in thalamic slices was due to the absence of the cortex in the latter, simplified preparation. In fact, after decortication, the simultaneity of spindle sequences throughout the thalamus is disorganized without, however, showing systematic propagation as in thalamic slices (Contreras et al., 1996). Also, compared to the simultaneous occurrence of spindle oscillations in the functionally intact brain, a diminished spatiotemporal coherence of spindle oscillations was observed during barbiturate anesthesia, when corticothalamic neurons display poor spontaneous activity, as well as during states of depressed cortex, produced by releasing a drop of highly concentrated K^+ acetate over the cortex (Destexhe et al., 1999).

5. Reticular neurons and inhibition of thalamocortical cells during cortical seizures

In essence, seizures with SW complexes at 3–4 Hz, as in absence epilepsy, are generated intracortically, and RE neurons faithfully follow each paroxysmal depolarizing shift (PDS) of neocortical neurons, which leads to inhibition of TC neurons (Steriade and Contreras, 1995) (see Fig. 1B). The opposite view, namely the intrathalamic generation of SW seizures (von Krosigk et al., 1993), was expressed in studies conducted in vitro, with isolated thalamic networks and absence of connections with the cerebral cortex. Also, in those in vitro studies (von Krosigk et al., 1993), the so-called ‘‘SW seizures’’, obtained by bicuculline injections in the thalamus, consisted in slowed (from 8 to 3 Hz) and regularly recurring spindle sequences, but not in paroxysmal

discharges. The slowing of spindles (but not SW seizures) after thalamic injection of substances blocking inhibitory processes, such as penicillin or bicuculline, has been earlier (Ralston and Ajmone-Marsan, 1956) and more recently (Steriade and Contreras, 1998) reported.

The role of neocortical neurons in generating SW seizures was first proposed (Steriade, 1974) on the basis that such paroxysms are focally detected in the cortical depth, sometimes without reflection at the cortical surface. In those experiments on behaving primates, tonic eye movements were associated with SW seizures at their onset and end, as in clinical absence epilepsy. The minimal substrate of SW seizures is the neocortex as they occur after thalamectomy (Steriade and Contreras, 1998). After disconnection from the thalamus in monkeys, cortical SW seizures were associated with impairment of awareness (Marcus et al., 1968), indicating that such seizures, accompanied by behavioral signs similar to those occurring in human absence epilepsy, may be generated in the absence of the thalamus. Multiple extracellular and intracellular recordings of neocortical neurons demonstrated the progressive intracortical build-up of SW and polyspike-wave (PSW) seizures, which are sequentially distributed through corticocortical circuits (Steriade and Amzica, 1994), reaching the thalamus only after 5–8 s (Neckelmann et al., 1998). This indicates that SW/PSW seizures originate within the cortex and are transferred to the thalamus only after a series of intracortical synaptic operations.

Simultaneous recordings of cortical and RE-neurons' activities revealed that spontaneous cortical SW seizures around 3 Hz are associated with spike-bursts in RE neurons, which follow each PDS in cortical mass potentials and are much longer (~200 ms) than before seizures (Steriade and Contreras, 1995). The same study used simultaneous recordings of cortical field potentials, RE-cell's unit discharges and intracellular activity of a TC neuron to show that, during cortical seizures with SW complexes at 3 Hz, the faithful following by RE cell of each cortical EEG "spike" is associated by IPSPs in the TC cell. In sum, then, GABAergic RE neurons participate actively during cortically generated SW seizures (Steriade and Contreras, 1995), which is corroborated by the increase in the ionic current underlying spike-bursts of RE cells in such seizures (Tsakiridou et al., 1995; Avanzini et al., 1999) and the fact that the Cd^{2+}-induced blockage of RE-cells' spike-bursts leads to a decrease in the ipsilateral SW activity (Avanzini et al., 1992).

The opposite, i.e., steady hyperpolarization and phasic, multiple IPSPs that do not lead to de-inactivation of spike-bursts, occurs in TC cells during cortically generated SW seizures (Steriade and Contreras, 1995). Thus, TC neurons do not transfer spike-bursts to the cortex. Similar findings on TC-cells' inhibition were reported in studies on animal models with inherited absence seizure, the genetic absence epilepsy in rats from Strasbourg (Pinault et al., 1998; Crunelli and Leresche, 2002), though the seizures investigated in this model are somewhat different since their frequency is twice higher (6–9 Hz) than in SW seizures of cats and primates. Here, a methodological issue should be stated, namely, only intracellular recordings can answer the question whether or not TC neurons burst during SW seizures as, with extracellular recordings, the so-called "spike-bursts" reported in some studies on SW seizures may just represent brisk firing of single action potentials due to prevalent excitation of TC neurons by corticofugal inputs during the depth-negative component of SW complexes. Such an activity does not, however, reflect LTSs de-inactivated by hyperpolarization of TC neurons since, intracellularly, these were trains of single action potentials at a depolarized level, triggered by depolarizing corticothalamic projections (see Fig. 7, B1, in Steriade and Contreras, 1995). Then, this firing pattern reflects excitation of TC neurons from cortex, rather than postinhibitory rebound spike-bursts.

Dual simultaneous intracellular recordings from the cortex and thalamus, in vivo, show that, during cortically generated seizures consisting of SW/PSW complexes at 2–3 Hz, most TC neurons display a steady hyperpolarization as well as phasic IPSPs, closely related to the "spike" component of cortical SW/PSW complexes (Fig. 13). At the

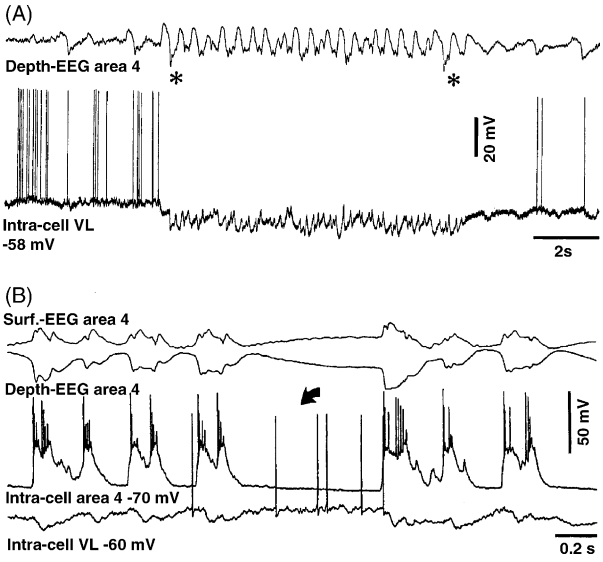

Fig. 13. Thalamocortical (TC) neurons are inhibited during cortically generated spike-wave seizure, and display phasic IPSPs but not spike-bursts. (A) Depth-EEG from cortical area 4 and intracellular recording of TC neuron from cat ventrolateral (VL) nucleus. Note hyperpolarization and phasic IPSPs in VL neuron throughout cortically generated spike-wave seizure. (B) Dual intracellular recordings from area 4 cortical neuron and TC neuron from VL nucleus, together with surface- 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 (PDSs) in cortical neuron, and phasic IPSPs related to cortical PDSs. Also note that, during a brief period of quiescence in cortical seizure (arrow), the hyperpolarization of TC neuron was removed and the neuron fired single action potentials. Modified from Steriade and Contreras (1995) and unpublished data by M. Steriade and D. Contreras.

end of the cortical seizure, TC neurons fire at high rates, as if they were released from the inhibition that occurred during the seizure. Similarly, following repetitive IPSPs related to cortical paroxysmal discharges, during a short period of quiescence of cortical activity occurring within the SW seizure, the TC neuron fires single potentials (Fig. 13B). The source of inhibition in TC cells should be searched in GABAergic RE neurons that fire spike-bursts during each PDS of cortical neurons (see Fig. 1B).

In conclusion, during cortically generated SW seizures, TC cells are steadily hyperpolarized and display phasic IPSPs that do not de-inactivate the LTSs. The inhibition of TC neurons, with increased membrane conductance, may explain the obliteration of signals from the external world and unconsciousness during these paroxysms.

Acknowledgements

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