



LTS cells in cerebral cortex and their role in generating spike-and-wave oscillations

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Abstract

Some types of epileptic seizures involve both thalamus and cerebral cortex, while other types can be evoked in the cerebral cortex without thalamic participation. We investigated the possible role of low-threshold spike (LTS) cortical neurons in the genesis of these intracortical seizures. We found LTS cortical neurons in cat area 5–7 *in vivo*, the properties of which could be modeled based on relatively weak densities of the T-type calcium channel. At the network level, a small minority of LTS pyramidal cells was sufficient to generate paroxysmal oscillations with spike-and-wave (SW) field potentials. These oscillations reproduce the properties of intracortical SW paroxysms observed in athalamic cats, such as the slow frequency (1.8–2.5 Hz). We suggest that calcium-mediated rebound mechanisms intrinsic to cerebral cortex can explain the genesis of intracortical SW activity. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Several types of epileptic seizures display spike-and-wave (SW) complexes at 2–4 Hz in the electroencephalogram. It has been shown that in some types of seizures, such as absence seizures, both cortex and thalamus are involved (reviewed in

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Refs. [5,14]). This type of “corticothalamic” seizures can be explained by thalamocortical loops, as shown by computational models [7]. However, other studies pointed to a neocortical origin of some SW seizures: (a) GABA_A-receptor antagonists induce SW seizures when applied to cerebral cortex [15,25], where as they fail to generate such paroxysms when injected to the thalamus [15,23,25]; (b) a majority of thalamic neurons are steadily hyperpolarized and completely silent during cortical SW seizures [18,22,24]; (c) seizure activity can be observed in cortex following thalamic inactivation or thalamectomy [19,21,25].

Thus, although some types of seizures involve both thalamus and cortex, other types of SW seizures seem to be purely intracortical. Here we analyze these intracortical SW seizures and compare their morphology to SW seizures obtained in the intact thalamocortical system. With computational models, we explore the hypothesis that intrinsic rebound mechanisms in some cortical cells could explain this form of seizure activity.

2. Methods

Multisite field potential recordings were obtained from areas 5–7 of cat cerebral cortex under barbiturate anesthesia. An array of bipolar tungsten electrodes was inserted in cortex, each channel measuring the difference between superficial and deep layers (typically between layer I and layers V–VI; see experimental procedures in Refs. [2,3]). Seizures were induced by injection of the GABA_A antagonist bicuculline (0.1 μ l, 0.2 mM) into deep layers of the cerebral cortex (see Methods in Ref. [25]). Intracellular recordings were also obtained in the same area of cat cerebral cortex in vivo using procedures described previously [4].

Computational models were designed based on the intrinsic firing properties of cortical neurons and the receptor types mediating their interactions. Cortical pyramidal neurons and interneurons were represented by single-compartment models including voltage-dependent Na⁺ and K⁺ currents described by Hodgkin–Huxley-type models (see Methods in Ref. [8]). Glutamatergic (AMPA) and GABAergic (GABA_A and GABA_B) receptors were modeled by kinetic models (see Methods in Ref. [9]). Extracellular field potentials were calculated based on synaptic and slow voltage-dependent currents in a one-dimensional array of pyramidal neurons—the contribution of fast Na⁺ and K⁺ currents and action potentials was assumed to be negligible (see details of the procedure in Ref. [7]).

3. Intracortical spike-and-wave oscillations

Multisite field potential recordings of cortical activity during barbiturate anesthesia are shown in Fig. 1. In control conditions, the activity consisted in barbiturate spindles, which are synchronized oscillations in the 7–14 Hz frequency range (Fig. 1A). After the application of bicuculline to the cortex, this activity developed into seizures with SW events, at a frequency of 2–4 Hz (Fig. 1B). This type of SW oscillation was

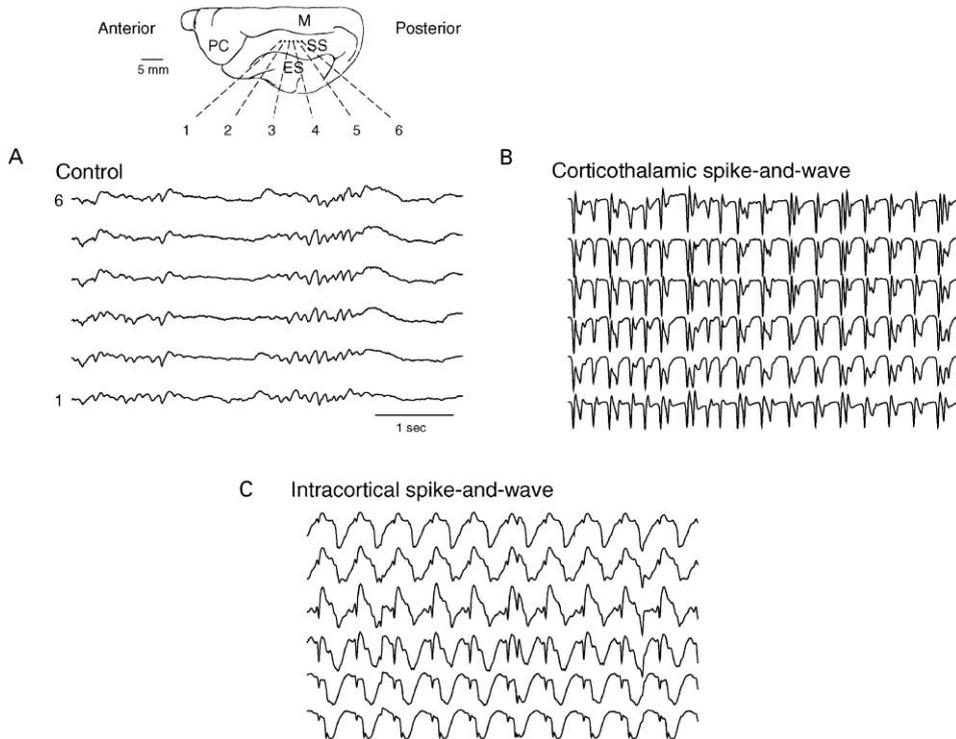


Fig. 1. Multisite field potential recordings in cat suprasylvian cortex. The scheme illustrate the disposition of recording electrodes SS suprasylvian gyrus; PC postcruciate gyrus, ES ectosylvian gyrus, M marginal gyrus). A. Spindle oscillations during barbiturate anesthesia. B. Spike-and-wave paroxysms in the same animal after injection of bicuculline in cortex (between electrodes 3 and 4). C. Spike-and-wave oscillation in the same brain area after complete thalamectomy (different animal as in A-B).

obtained in the intact thalamocortical system (even in the absence of bicuculline application) and will be referred to as the “corticothalamic SW”.

A complete thalamectomy was performed in three cats (procedures and histological controls described in Ref. [25]). Similar to the above case, application of bicuculline to the cerebral cortex after thalamectomy led to the development of seizures with SW patterns (Fig. 1C). But the morphology of the SW was different as the negative “spike” was less pronounced (compare B and C in Fig. 1) and the oscillation frequency was slower (about 1.8 Hz in Fig. 1C; range 1.8–2.5 Hz).

4. Rebound bursting activity in cerebral cortex

To investigate if rebound bursting activity similar to thalamus is present in cerebral cortex, we performed *in vivo* intracellular recordings in the same area of neocortex from which the intracortical SW was recorded. We observed low-threshold spike

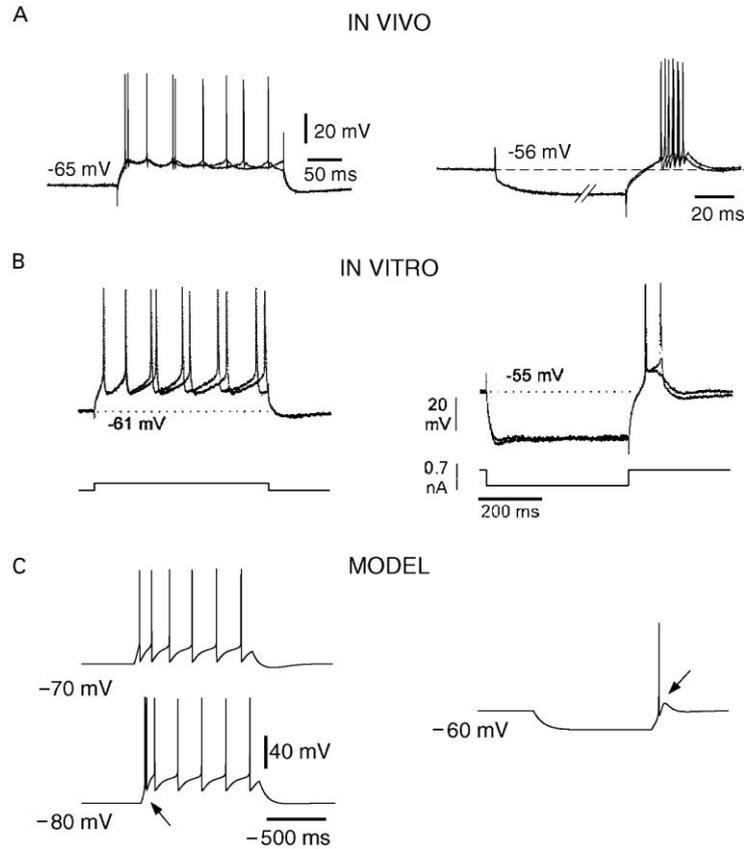


Fig. 2. Rebound bursting properties of cortical pyramidal cells. A. Rebound bursting cell from cat cerebral cortex in vivo. B. Rebound bursting cell from guinea-pig frontal cortex in vitro (adapted from Ref. [6]). C. Model pyramidal cell comprising I_{Na} , I_K , I_M and I_T currents. Left: repetitive firing with adaptation following injection of depolarizing current (0.1 nA). Right: rebound burst response at the offset of a hyperpolarizing current pulse (-0.1 nA; the pulse was 200 ms in A and was truncated for clarity). Arrows indicate bursts of action potentials mediated by I_T .

(LTS) activity in a significant fraction (about 10%) of intracellularly recorded cells (Fig. 2A). These LTS neurons generated adapting trains of action potentials in response to depolarizing current injection (Fig. 2A, left panel), similar to the classic “regular-spiking” response of cortical neurons [1]. In addition, they generated a burst of action potentials in response to injection of hyperpolarizing current pulses (Fig. 2A, right panel). This property was also identified in deep layers of guinea-pig cerebral cortex in vitro [6] (Fig. 2B) and was shown to be due to the presence of the T-type (low-threshold) calcium current I_T .

In the model, we have attempted to reproduce these intrinsic firing properties based on single-compartment representations of pyramidal neurons. To generate the classic “regular-spiking” behavior (Fig. 2C, -70 mV), the model included three

voltage-dependent currents represented by Hodgkin–Huxley [17]-type kinetics: a slow voltage-dependent K^+ current termed I_M (kinetics from Ref. [20]), as well as the I_{Na} and I_K currents for action potential generation (kinetics from Ref. [27]). In addition, to generate rebound bursting behavior, the T-type calcium current was included (kinetics from Ref. [10]) and its peak amplitude was adjusted to match voltage-clamp recordings of this current in pyramidal neurons [6]. A density of T-channels of 0.8 mS/cm^2 was needed to match the relatively small amplitude of this current measured in pyramidal neurons.¹ Using this density, the model could generate weak rebound bursts at the offset of hyperpolarizing current (Fig. 2C, -60 mV). From hyperpolarized levels, this model generated an initial burst followed by an adapting train of action potentials (Fig. 2C, -80 mV), which is a feature often observed in neocortical neurons [1].

Simulations were also performed using more complex morphological models including dendrites (not shown) and it was revealed that the ability to generate rebound bursts depended on the somatodendritic distribution of I_T and the hyperpolarization-activated current I_h , but the latter current was not strictly necessary and was therefore not included in the single-compartment model. We conclude that a relatively weak density of T-current, in addition to I_{Na} , I_K and I_M , confers LTS genesis to the model pyramidal cell, consistent with recordings of LTS cortical neurons in vivo and in vitro.

5. Model of intracortical spike-and-wave

The network impact of LTS neurons was investigated in a network consisting of excitatory (pyramidal) neurons and interneurons, whose connectivity was mediated by AMPA, $GABA_A$ and $GABA_B$ receptors (Fig. 3A). In control conditions, no oscillatory behavior could be observed if a significant proportion of pyramidal neurons (up to 20%) had LTS properties similar to Fig. 2C. The same proportion of LTS pyramidal neurons in the thalamocortical model [7] did not alter the genesis of spindle oscillations (not shown). This is due to the fact that in control conditions, all cells in the network generate brief discharge patterns, which lead to the activation of IPSPs that are dominated by the $GABA_A$ component, with negligible $GABA_B$ activation. Because of the relatively weak conductance of I_T in LTS cortical cells, $GABA_A$ -mediated IPSPs were not sufficient to activate any rebound burst in these neurons.

On the other hand, when $GABA_A$ -mediated inhibition was suppressed, mimicking the effect of bicuculline, the disinhibited network generated sustained oscillations (Fig. 3B). Due to the removal of fast inhibition, all cells in the network produced prolonged discharge patterns. The prolonged discharge of interneurons was optimal

¹ The peak amplitude of I_T in pyramidal neurons of guinea-pig cerebral cortex is of about $0.4\text{--}0.8 \text{ nA}$ [6], which is small compared to the peak amplitude of I_T in other cell types, for example it is $5.8 \pm 1.7 \text{ nA}$ in rat thalamic relay cells [10].

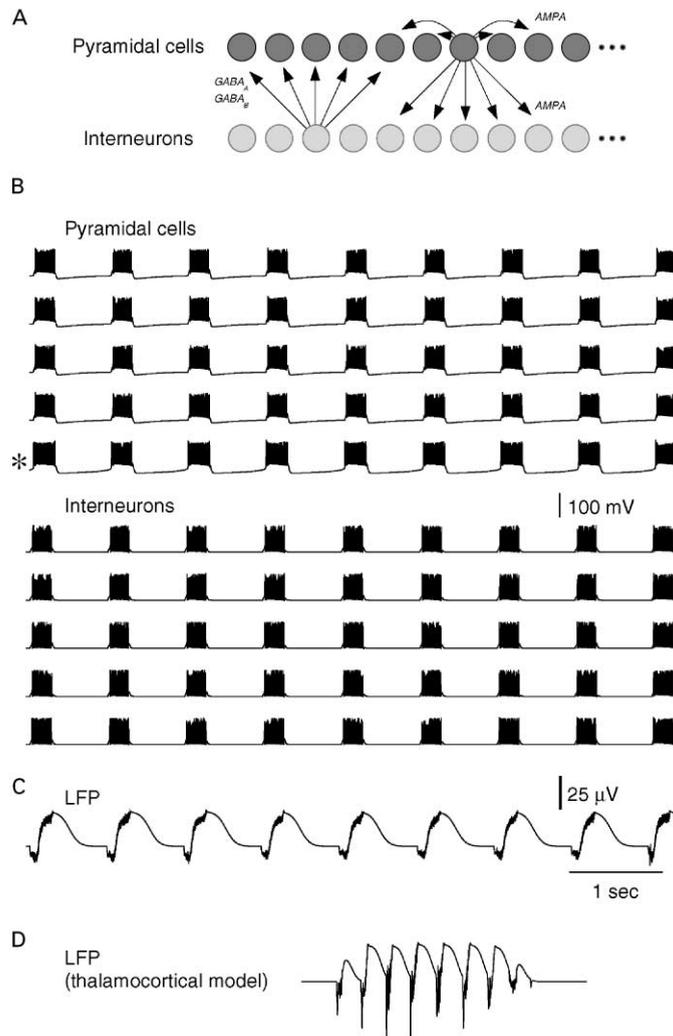


Fig. 3. Spike-and-wave oscillations in a network of cortical neurons. A. Scheme of the network: all pyramidal cells had I_{Na} , I_K and I_M currents, and 5% of pyramidal neurons were rebound bursting cells containing an additional weak density of T-current (as in Fig. 2C). B. Oscillatory activity after removing GABA_A connections. All cells displayed prolonged discharges in phase, separated by periods of silences dominated by K^+ currents, at a frequency of ~ 1.3 Hz. * indicates a rebound bursting pyramidal cell. No thalamic cells were included in this simulation. C. Field potentials calculated from the same simulation showed spike-and-wave complexes. D. Field potentials of the thalamocortical model of SW (taken from Ref. [7]) are shown for comparison (same calibration as C).

to activate GABA_B-mediated inhibition in pyramidal cells, in agreement with the highly nonlinear activation properties of these receptors [11,26]. If the GABA_B conductance was sufficiently large (0.05–0.1 μS), GABA_B-mediated IPSPs could activate a rebound burst in the pyramidal neurons that contained I_T , similar to

current injection in Fig. 2. The oscillation therefore consisted of GABA_B IPSP-rebound sequences, in which the rebound of the entire network was triggered by a minority of pyramidal neurons containing I_T . A small proportion of LTS pyramidal cells, as small as 5%, depending on the connectivity used, was sufficient to generate slow oscillations in the disinhibited network.

In calculated extracellular field potentials, this slow oscillation generated SW patterns. The synchronized discharge of all cells in the network generated a negative “spike” component (Fig. 3C). The subsequent activation of GABA_B IPSPs induced a period of silence in the network, during which pyramidal neurons were hyperpolarized by K⁺ currents (a mixture of GABA_B-mediated IPSPs and voltage-dependent K⁺ currents). These outward currents generated a slow positive “wave” in the field potentials (Fig. 3C). Therefore, the disinhibited cortical network can generate on its own a form of SW oscillation, by mechanisms similar to those described previously in the thalamocortical network (see Ref. [7]).

The intracortical mechanisms leading to SW in this model are based on the following sequence of events: (a) due to suppressed GABA_A-mediated inhibition, the disinhibited cortical network generated prolonged discharges. These events generated a negative “spike” in simulated field potentials. (b) Due to the prolonged firing of interneurons, powerful GABA_B-mediated IPSPs hyperpolarized pyramidal cells, stopping their discharge. These slow IPSPs, as well as other slow K⁺ currents maximally activated due to the prolonged firing, generated a positive slow “wave” in field potentials. (c) At the offset of GABA_B IPSPs, a fraction of pyramidal cells generated a rebound burst, entraining the entire network in prolonged discharges and restarting the oscillation cycle.

Two additional properties of this model are consistent with experiments. First, the oscillation frequency was slower in the “intracortical SW” compared to the “thalamocortical SW” (1.3 Hz compared to 2–4 Hz in Ref. [7]—compare C and D in Fig. 3). This effect was, here, due to the relatively small conductance of I_T in pyramidal cells, which gave rise to a significant delay before rebound and consequently a slower oscillation frequency. Second, the “spike” component was less prominent here compared to the thalamocortical model (compare C and D in Fig. 3). In the thalamocortical model, the pronounced negative “spike” was due to thalamic EPSPs that preceded other EPSPs in pyramidal cells (see Fig. 8B in Ref. [7]). These events were of course absent here, leading to a less prominent negative “spike” component, in agreement with Fig. 1C.

6. Discussion

We have compared spike-and-wave paroxysms in the intact thalamocortical system with those generated intracortically. The intracortical SW was similar to previous observations in isolated cortex or in athalamic preparations in cats [19,21,25].² These

² However, intracortical spike-and-wave activity could not be observed in rats [28].

intracortical SW paroxysms have a different morphology compared to SW seizures in the intact thalamocortical system. They are slower in frequency (1–2.5 vs 2–4 Hz) and the “spike” component is less prominent. This is also consistent with previous observations [19,21]. Intracellular recordings should be performed during the intracortical SW to further analyze the similarities and differences with thalamocortical SW.

By recording in the same area of cerebral cortex, we have shown that a minority of recorded cells displays rebound burst properties. This is consistent with previous observations in different animals and brain areas, where some pyramidal neurons express the T-type Ca^{2+} current and display rebound burst activity [6,12,13,16]. Simulations indicate that a relatively weak overall density of T-current (estimated here as about 0.8 mS/cm^2), consistent with experimental measurements [6], can account for the properties of these LTS cortical neurons.

By using simple models of cortical networks in which a minority of pyramidal neurons were LTS neurons, we showed that the network can display self-sustained slow oscillations when GABA_A receptors are suppressed. The extracellular field potentials calculated for these slow oscillations display negative “spikes”, generated by the population firing, alternating with slow positive “waves”, which were here mediated by GABA_B IPSPs and voltage-dependent K^+ currents. The slow frequency of these intracortical SW oscillations was due to the low T-current conductance in the LTS pyramidal cells. The model therefore predicts that a relatively weak rebound mechanism in a minority of cortical pyramidal neurons is sufficient to generate a slow network oscillation with SW field potentials. Similar to the mechanism proposed previously for thalamocortical spike-and-wave [7], the oscillation is generated by rebound firing following K^+ -mediated hyperpolarizing events.

The coexistence of two different SW mechanisms (intracortical vs. corticothalamic) should be investigated by future models and experimental studies. For example, this model should be integrated with a thalamocortical model of SW [7] to see under what conditions intracortical loops prevail over corticothalamic loops, which may help to explain the rich variety of paroxysmal patterns observed experimentally in different conditions.

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