Waking–Sleep Modulation of Paroxysmal Activities Induced by Partial Cortical Deafferentation

We investigated the dependency of electrical seizures produced by cortical undercut upon behavioral states of vigilance in chronically implanted cats. Experiments were performed 1–12 weeks after white matter transection. Multisite field potentials and intracellular activity were recorded from suprasylvian and marginal gyri. Paroxysmal activity developed within days and consisted of spike-wave complexes at 3–4 Hz occurring during the waking state (correlated with eye movements), being enhanced during slow-wave sleep (SWS) and blocked during rapid eye movement (REM) sleep. Prolonged hyperpolarizing events were seen not only during SWS (which is the case in normal animals) but also during both waking and REM, thus resulting in bimodal distribution of the membrane potential in all 3 natural states of vigilance. The increased synchrony of field potential activity expressed by shorter time of propagation over the cortical surface and the tendency toward generalization are ascribed to changes in intrinsic neuronal properties and potential disinhibition following cortical undercut.

Keywords: cortical undercut, electrical seizures, field potentials, intracellular recordings, waking–sleep states

Introduction

Acute seizures following cortical trauma produced by penetrating wounds attain up to 80% of patients in the first 24 h (Dinner 1993), and chronic posttraumatic epilepsy was reported in over 50% of cases (Salazar and others 1985). Trauma elicits partial neocortical deafferentation and, consequently, decreases input signals, which can result in enhanced intrinsic and synaptic excitability of individual neurons (Turrigiano and others 1998; Desai, Nelson, and Turrigiano 1999). Chronic neuronal hyperexcitability and epileptogenesis have been experimentally demonstrated in isolated cortical islands in vivo (Burns 1951; Sharpless and Halpern 1962) and in neocortical slices maintained in vitro after cortical injury (Prince and Tseng 1993; Hoffman and others 1994; Prince and others 1997; Li and Prince 2002). After isolation, the neocortex becomes progressively more excitable and may develop prolonged ictal events within several weeks. Computational models of posttraumatic epileptogenesis suggested that paroxysmal discharges are due to changes in intrinsic properties of pyramidal cells and enhanced N-methyl-D-aspartate synaptic conductances (Bush and others 1999; Houweling and others 2005).

Acute experiments performed under anesthesia, in vivo, showed that partially deafferented neocortex displays changes in long-distance synchrony and paroxysmal activity that occurs 2–3 h after cortical undercut and arises from enhanced intrinsic and synaptic neuronal responsiveness, increased incidence of spontaneously bursting neurons, and slight reduction in inhibitory processes (Topolnik and others 2003a, 2003b). Recordings under anesthesia in a model of chronic partial cortical deafferentation showed that, following the undercut, the neocortex displays progressively increased signs of paroxysmal activity, expressed by progressively enhanced amplitudes and synchrony of spike-wave/polyspike-wave (SW/PSW) complexes (Nita and others 2005).

The aim of the present study was to investigate the relations between paroxysmal activity in the deafferented cortex and natural states of vigilance in chronically implanted cats, with the hypothesis that the incidence and widespread feature of such electrical seizures would be mainly expressed during slow-wave sleep (SWS). It was indeed shown that cortical seizures with SW complexes prevalently occur during early SWS stages in behaving monkeys (Steriade 1974) and that the slow sleep oscillation (0.5–1 Hz) may develop, without discontinuity, into electrographic seizures in cats (Steriade and others 1998), probably due to highly synchronous activities in corticothalamic systems. Clinically too, SWS is considered as a potent activator of epileptiform discharges (Gigli and others 1992; Dinner 2002; Niedermeyer and Lopes da Silva 2004), whereas REM sleep, with its asynchronous cellular discharge pattern, is resistant to the propagation of epileptic electroencephalogram (EEG) potentials (Shouse and others 2000). We then used field potentials and intracellular recordings in chronic experiments in vivo to study the evolution of electrical paroxysms induced by cortical deafferentation, up to 3 months following the undercut, to determine the spatiotemporal development of posttraumatic seizures with respect to the initial cortical insult, to quantify at different stages the transformation from the normal slow oscillation to paroxysmal patterns, and to determine how epileptic activities are modulated by the 3 major states of vigilance, waking, SWS, and REM sleep.

Materials and Methods

Animal Preparation

Experiments were performed on 6 chronic cats of both sexes. Surgical procedures were carried out in sterile condition, following a premedication with acepromazine (0.3 mg/kg intramuscularly [i.m.]), butorphanol (0.3 mg/kg i.m.), atropine (0.05 mg/kg i.m.), and ketamine (20 mg/kg i.m.), under barbiturate anesthesia (30 mg/kg intravenously). The level of anesthesia was continuously monitored by the aspect of the EEG and cardiac frequency (aiming 90–110 beats/min). Oxygen saturation of the arterial blood and end-tidal CO₂ was also monitored. General surgical procedures included cephalic vein canulation for systemic liquid delivery (lactated Ringer’s solution 5–10 ml/kg/h) and lidocaine (0.5%) infiltration of all pressure points or incision lines. Body temperature was maintained between 37–39 °C with a heating pad.

Craniotomy was used to expose the cerebral cortex, and a large undercut of the white matter below the suprasylvian gyrus (13–15 mm posteroinferiorly and 3–4 mm mediolaterally) was used to produce...
partial cortical deafferentation by transecting the thalamocortical projections. A standard blade (3 mm width and 14 mm long) was inserted in the posterior part of suprasylvian gyrus perpendicular to its surface for a depth of 3–4 mm, then rotated 90° and advanced rostrally along the gyrus parallel to its surface for a total distance of 14 mm, then moved back, rotated 90°, and removed from the same place where it was entered (see Fig. 1A–C). The use of a custom-designed knife ensured a similar extension of the lesion. Thus, the anterior part of the undercut cortex was relatively intact, and the white matter below the posterior part of the gyrus was transected, creating conditions of partial cortical deafferentation.

Coaxial bipolar macroelectrodes (with the tip in the cortical depth at about 0.8–1 mm and the ring placed at the cortical surface) were placed in various cortical areas in different configurations. In 3 cats, a recording chamber allowing intracellular penetrations of micropipettes was placed over the intact dura, above the anterior part of the suprasylvian gyrus. Additional pairs of electrodes were placed around the orbit and neck muscles to monitor the states of vigilance by recording the electrooculogram (EOG) and electromyogram (EMG). The calvarium was reconstituted using acrylic dental cement, and a few bolts were placed in the cement to allow nonpainful fixation of the cat’s head in a stereotaxic frame. Animals were kept under observation up to the full

**Figure 1.** Experimental paradigm. (A) Lateral view of the left cerebral hemisphere. Experiments were performed on chronically implanted cats with complete transections of white matter below the suprasylvian gyrus. Red arrows indicate the place where the knife used to perform the undercut entered the cortex. (B) Frontal and (C) sagittal brain sections in Nissl staining used to ascertain the extent of cortical deafferentation. (D) EEG recordings in the deafferented (undercut) and intact cortex (areas 5 and 7 on the right side) 6 h after surgical proceeding (under anesthesia) and 4 days later (during SWS). Activity in the acutely partially deafferented cortex (area 5) is dominated by highly increased amplitude of the cortical slow oscillation (~1 Hz), compared with normal slow oscillation in the opposite hemisphere (see also the left panel in E). (E) FFT power spectra. Four days later, during SWS, EEG in the undercut consists of a mixture of ~1 Hz activity (D) and a faster activity of about 3–4 Hz (*).
recovery, and they received analgescic medication (anafen 2 mg/kg subcutaneously) for the next 48–72 h.

After a recovery period (2–3 days), cats were trained to stay in the frame for 1–2 h/day. After a few days of training, cats started to sleep in the frame and they displayed clearly identifiable states of waking, SWS, and REM sleep. Criteria used to distinguish between different waking states were the level of the tonic EMG activities (high during wake, decreased during SWS, and very low during REM sleep) and the occurrence of eye movements during wake and REM.

**Electrophysiological Recordings**

EEG recordings, started 3–5 days after surgery, were performed 2–5 times per week and lasted up to 3 months. Intraocular recordings of cortical neurons were obtained with glass micropipettes (tip diameter <0.5 μm) filled with potassium acetate (3 M, in situ impedance 35–50 MΩ) after small perforations in the dura were carefully made. The chamber was filled with warm sterile solution of 4% agar to enhance the stability of the recordings. Only stable recordings with resting membrane potentials more negative than ~60 mV, overshooting action potentials, and input resistances >20 MΩ were kept for analysis. The intracellular signals were passed through a high-impedance amplifier with an active bridge circuitry (20 kHz sampling rate) and stored for off-line analysis.

As a rule for intraocular recordings, 2–3 recording sessions, each lasting for 2–3 h, were performed daily and usually contained periods of waking, SWS, and REM. The cats were not deprived of sleep between recording sessions, and during recordings they could move their limbs and make postural adjustments. During recording session, animals were monitored using a night-shoot video surveillance camera.

Behavioral seizures were considered an “end limit point” of these experiments, as consented with the local ethic committee. Three cats displayed small localized muscular jerks and abnormal tail wagging during waking state, and 1 cat displayed generalized seizures. At the end of experiments or at the first sign on clinically manifest seizures, the cats were given a lethal dose of intravenous sodium pentobarbital (50 mg/kg). After experiments, the brains were removed, and the extension of the undercut was verified on Nissl stained (thionine) 80-mm brain sections (Fig. 1A–C). All experimental procedures were performed in accordance with the guidelines published in the National Institutes of Health guide for the care and use of laboratory animals, with the proceedings and politics of the local committee for animal protection, and all experimental procedures were approved by the committee for animal care of Laval University.

**Data Analysis**

Wave-triggered averages were calculated taking as reference the segment with the steepest deflection in the EOG during eye movements and averaging equal windows around that point from both EEG and EOG channels (see Fig. 2B). EEG power in the 3- to 5-Hz range was quantified by the area under the fast Fourier transformation (FFT) graph of field EEGs (see Fig. 5C). Means of comparative data were statistically evaluated with paired Student’s t-test. Differences between means were considered significant at $P < 0.05$.

Autocorrelograms were generated on successive windows of 1-s length (Fig. 6D), and the area under the autocorrelation graph on a 100-ms time-window (shifted from the zero line with 250 ms corresponding to the dominant +4 Hz frequency) was measured and displayed as in Figure 6A. Cross-correlograms of different EEG channels (Figs 3F and 7B) were computed on 30 s of stable recording and the time shifts measured and averaged between different individuals. In Figure 3B, electrode 5 was taken as reference for all cross-correlograms between pairs of EEG electrodes placed over intact cortical areas, whereas for the undercut the reference was the electrode 12 because previous studies in chronic undercut under anesthesia shown a propagation of seizures from the more intact to the more deafferented cortex (Nita and others 2005).

Histograms of the time duration of ictal events and interictal periods (Fig. 4A) were obtained from epochs of 3 min of stable and clearly identifiable waking EEG recordings and displayed with a 1-s bin width. Histograms of membrane potential distribution (Fig. 8C) were created for successive periods of 10 s by counting the number of samples with bins of 1 mV. The peaks of distribution that corresponded to the most probable mode of membrane potential were taken as the level of membrane potential. The peri-spike histograms (Fig. 8F) were obtained over 5 min epochs, taking as time reference each action potential in the intracellular recording and counting the level of the membrane voltage with a bin width of 5 ms.

**Results**

**Development of Seizures and Spatiotemporal Properties of Paroxysmal Activities**

Six hours following acute partial cortical deafferentation, recordings performed under anesthesia showed paroxysmal-like field potentials in the anterior part of the suprasylvian gyrus, consisting of high-amplitude slow waves with the morphological features of interictal spikes and with ripples superimposed on their depth-negative phase (Fig. 1D). Their amplitude was at least twice as high as the normal slow oscillation recorded in the contralateral hemisphere, and the dominant frequency was around 1 Hz as revealed by the FFT power spectra (Fig. 1E, left panel). The first peak was centered around 1 Hz, similar to the activity observed during the acute period, whereas the second peak represented a faster rhythm in the 3- to 4-Hz domain (marked with * in Fig. 1D).

Several days later, the EEG recorded during natural SWS from the anterior part of the undercut cortex still displayed a slow oscillation with a larger amplitude, compared with the contralateral cortical areas (Fig. 1D), but 2 clearly distinct frequency peaks appeared in the power spectra (Fig. 1E, right panel). The first peak was centered around 1 Hz, similar to the activity observed during the acute period, whereas the second peak represented a faster rhythm in the 3- to 4-Hz domain (marked with * in Fig. 1D).

These ictal events were observed in all recorded animals and consisted of patches of ample 3- to 4-Hz SW complexes occurring intermittently during the waking state (Fig. 2A) when it was related with eye movements (Fig. 2B) and continuously during SWS. Deflection on EOG recordings appeared at the beginning and/or at the end of the ictal events (see lead 14 in Fig. 2A, B), in a similar manner with the eye movements clinically observed in absence epileptic seizures in humans (Penfield and Jasper 1954; Bickford and Klass 1964).

Polygraphic recordings by means of EEG electrodes placed over multiple areas in the deafferented cortex as well as in the contralateral cortex were performed from day 5 up to day 120 to study the distribution of ictal events with respect to the original site of trauma. This evolution is depicted during the waking state in Figure 3A. Initially, paroxysmal activities were exclusively present over areas around the undercut cortex, especially in the marginal gyrus of the ipsilateral hemisphere (leads 5, 7, and 9 and during days 5 and 10 in Fig. 3A) and in some homotopic marginal foci of the contralateral hemisphere (lead 10 on day 5 in Fig. 3A). Besides the marginal gyrus, paroxysmal activity was also detected around the undercut, within the most posterior part of the suprasylvian gyrus (see lead 4 in Fig. 5). During later stages, all cats exhibited a tendency toward generalization over the whole cortical surface, and the deafferented suprasylvian gyrus displayed only after ~30–40 days this type of generalized paroxysmal activity (day 45 in Fig. 3A). Average time delays and peak level of cross-correlograms computed between different cortical EEG electrodes from day 5 to day 90 (Fig. 3B) indicated that in the undercut the propagation of 4-Hz activities regularly has an anteroposterior pattern, whereas in the intact cortex seizures start around the deafferented cortex (electrodes 7 and 9) with a more
heterogeneous dynamics. A tendency toward faster propagation (smaller time lags between electrodes) and increased correlation, both in the intact and the undercut cortex, was observed with time from day 5 to day 90.

The quantification of the number and time duration of ictal events during the waking state was computed based on 3 min recordings from day 4 up to day 120 (Fig. 4A). Although the duration of individual ictal events remained quasi-constant (around 5 s), their number showed a plateau in the first 2 weeks; thereafter, it significantly decreased up to 30% of the original value and then increased again up to 75% of the initial number, remaining constant afterward for long periods of time (Fig. 4B). This behavior was clearly observed in 4 over 6 experimental animals that displayed easily identifiable ictal episodes.

**Sleep Modulation of Seizures**

Polygraphic recordings during natural waking and sleep states showed that the 4-Hz ictal events occurred during waking became quasi-continuous during SWS, whereas they were completely absent during periods of REM sleep (Fig. 5A). This behavior was also reflected in the peak of the field EEG power spectra that was increased three times during SWS, compared with the waking state, and disappeared during REM sleep (Fig. 5B). However, low-amplitude slow waves were occasionally present during REM sleep, which is not the case in the intact cortex. Quantifications were performed by measuring the area corresponding to the 3- to 5-Hz window in the power spectra from 10 successive recordings between day 5 and day 15 in each of the 6 chronically implanted animals (Fig. 5C). Statistically significant differences (Student’s t-test, \( P < 0.05 \)) were observed in the amount of 4-Hz activities between waking and REM state as well as between SWS and REM, whereas the 30% increase of power during SWS compared with waking did not reach statistical significance level.

Autocorrelograms of EEG activity (Fig. 6) indicated a dominant frequency oscillation \( \sim 4 \text{ Hz} \) (220-250 ms width of the main peak in the autocorrelogram) during both SWS and wake, more reliable in time during SWS compared with wake. This was

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Figure 2. Relation of ictal events with eye movements. (A) Polygraphic recordings in a chronically implanted cat with a cortical undercut on the left side (depicted as a gray box on the schema) during wake. Ictal events with frequencies in the 3- to 4-Hz time domain are associated with ocular movements at the beginning and at the end of the seizure. (B) Multiple EEG individual sweeps obtained taking as reference the steepest drop in the EOG deflection. Spectral decompositions of single EEG trials (on 4 s windows before and after the EOG deflections) point out the occurrence of seizures after the eye movements both by the expression of a 4-Hz peak in the FFT and by the increase in the FFT area over the 2- to 6-Hz domain. (C) Ictal events expanded from the underlined gray box in (A) show typical spike-wave complexes.
Figure 3. Topographic distributions of ictal events over the cortical surface from day 5 to day 45 during wake. (A) Polygraphic recordings in chronic cat with deafferented left suprasylvian gyrus (depicted as a gray box) indicate that paroxysmal activities are present initially in the cortical areas adjacent to the deafferented cortex, and they display a tendency toward generalization in time over the whole cortical surface. (B) Average time delays and peak level of cross-correlograms performed between different cortical EEG electrodes from day 5 to day 90 in 3 different experimental animals. In the intact cortex electrode 5 was taken as reference, whereas in the undercut the reference was electrode 12. In the undercut the propagation of 4-Hz activities regularly displayed an anteroposterior pattern, whereas in the intact cortex seizures started around the deafferented cortex (electrodes 7 and 9). Data indicate a tendency toward faster propagation and increased correlation with time both in the intact and the undercut cortex.
replaced during REM sleep by an uneven correlogram containing both fast activities and some slow waves (Fig. 6B). Measuring the area under each single autocorrelogram corresponding to sequential 1-s epochs of recording, we determined that paroxysmal activities were increased during SWS compared with wake and strikingly diminished during REM sleep (Fig. 6A).

Seizures started successively in different EEG leads during the waking state (with a delay decreasing with time, from day 1 to day 120), whereas during SWS they occurred with much shorter delays (Fig. 7A; electrodes 5, 6: 45.21 ± 15.24 ms in waking vs. 35.02 ± 3.89 ms in SWS; electrodes 5–7: 872.48 ± 315.14 vs. 189.45 ± 72.45 ms; electrodes 5–8: 912.35 ± 478.12 vs. 213.35 ± 65.14 ms). They originated at the border between the intact and the deafferented suprasylvian gyrus, generally displayed highest amplitudes in the marginal gyrus, and propagated ipsilaterally as well as to the contralateral marginal gyrus. Occipital (posterior marginal) areas were involved afterward, first on the lesion side, then contralaterally. Correlations between activities recorded by different EEG electrodes over marginal gyri (Fig. 7B) were used to compute the time lag of SW propagation during wake and SWS and to quantify the time delays in all recorded experimental animals (Fig. 7C). In all cases, a quasi-simultaneous occurrence of SW complexes occurred during SWS (electrodes 5, 6: 1.25 ± 0.85 ms; electrodes 5–7: 1.04 ± 0.97 ms; electrodes 6–8: 1.04 ± 0.89 ms; electrodes 7, 8: 1.2609 ± 0.93 ms), whereas paroxysmal activities required a longer time during waking (electrodes 5, 6: 5.02 ± 3.89 ms; electrodes 5–7: 13.21 ± 4.01 ms; electrodes 6–8: 9.4512 ± 4.12 ms; electrodes 7, 8: 1.2672 ± 3.97 ms).

**Intracellular Correlates of Seizures**

Intracellular recordings were performed in the anterior part of the suprasylvian gyrus from day 14 to day 21 after cortical deafferentation. Of 23 recorded neurons, 7 underwent a transition from one state of vigilance to another. Four neurons were recorded during all 3 states of vigilance (Fig. 8A), and all of them were identified as regular-spiking neurons following depolarizing current pulses applied to the soma. At variance with our previous intracellular recordings in naturally awake and sleeping nonepileptic cats, in which rhythmic hyperpolarizations within the frequency of the slow oscillation exclusively occurred during SWS (Steriade and others 2001), the present data showed hyperpolarizing events during all states of vigilance. They were manifest during both SWS and waking (overall incidence: 1.64 ± 0.7/s and 1.26 ± 0.6/s, respectively), but
short-duration hyperpolarizations also occurred during REM sleep (Fig. 8B). The incidence of these events pointed out a bimodal distribution of the values of the membrane potential in all 3 states of vigilance (Fig. 8C).

Based on their time duration calculated at the half of their amplitude, these hyperpolarizing events were grouped in 2 clusters: short-length (<150 ms) and long-length (>150 ms).

Whereas the first ones displayed a quite constant incidence during all states of vigilance—SWS: 0.85 ± 0.17/s, REM: 0.51 ± 0.15/s, waking: 0.83 ± 0.15/s—the latter resembled the periods of long-lasting disfacilitation that normally takes place during the cortical slow sleep oscillation and were present during waking (0.43 ± 0.13/s), enhanced during SWS (0.78 ± 0.14/s), and absent during REM sleep (0.02 ± 0.01/s; Fig. 8D).
Furthermore, all recorded neurons displayed an enhanced excitability consisting in a sharp transition between the "up" and the "down" states during SWS and waking. This was related to the occurrence of spike bursts. Indeed, peri-spike histograms of intracellular activities indicated a preference toward bursting behavior of cortical neurons during SWS and waking, whereas neurons discharged tonically during REM sleep (Fig. 8E).

Discussion
The main findings reported in the present study are as follows: 1) following partial deafferentation of suprasylvian gyrus, recurrent seizures with 4-Hz SW complexes, first localized in territories contiguous to trauma, thereafter generalized over the whole cortical surface, were observed in all experimental animals; 2) the incidence of ictal events was modulated by the state of vigilance, occurring during the waking state, being enhanced during SWS, and absent during REM sleep; 3) the propagation of seizures increased during SWS compared with waking; and 4) all cortical neurons recorded in this study expressed a bimodal distribution of $V_m$ values, due to the presence of hyperpolarizations during all states of vigilance, more obvious during SWS and waking.

Several factors may account for the increased propensity of seizures following the cortical insult produced by undercut. Although both an acute raise of $[\text{K}^+]_o$ (Moody and others 1974) triggering a $K^+$-mediated increase in the hyperpolarization-activated depolarizing current ($I_h$) leading to cortical paroxysmal activities (Timofeev and others 2002) and an increase in the concentration of the extracellular glutamate leading to seizures (Sakowitz and others 2002) could not be envisaged in chronic conditions, trauma-induced chronic hyperexcitability and focal epileptogenesis could be explained by the homeostatic plasticity mechanisms upregulating the neuronal excitability (Houweling and others 2005).

The progressive development of seizures in the partially deafferented cortex is in line with earlier studies showing that the chronically isolated neocortex develops hyperexcitability and focal epileptogenesis (Echlin and Battista 1963). Although spontaneous bursts appear a few days after isolation, they occur more frequently during subsequent days and weeks (Grafstein and Sastry 1957; Sharpless and Halpern 1962; Burns and Webb 1979).

Chronic activity blockade enhances $\text{Na}^+$ currents and reduces $\text{K}^+$ currents, resulting in enhanced responsiveness of pyramidal neurons to current injection (Desai, Rutherford, and Turrigiano 1999). The isolated cortex develops an increased susceptibility to epileptiform activity that is similar to the disuse supersensitivity in some structures deprived of afferent inputs (Sharpless 1969). Some additional mechanisms for an increased synaptic drive following axotomy could also be envisaged, such as axonal regeneration and sprouting of axonal arborizations of pyramidal cells onto neighboring neurons (Chen and others 2002).

The initial and prevalent occurrence of paroxysmal activity in cortical territories located "outside" the most deafferented (suprasylvian) cortex, namely the marginal gyrus and parts of the suprasylvian gyrus posterior to the cortical undercut (see Figs 2 and 3), may be explained by the fact that only relatively intact neurons, which are found in the vicinity of the isolated cortex, are expected to promote paroxysmal activity. This may partially arise from a transformation of regular spiking into intrinsically bursting neurons due to $K^+$ accumulation (Jensen and Yaari 1997). Synaptic inputs to neurons with an enhanced
intrinsic excitability, such as bursting neurons, may promote the initial paroxysmal discharges in sites outside the disconnected cortex.

The activating properties of SWS on epileptiform discharges should be ascribed to highly synchronized oscillations in reciprocal thalamocorticothalamic systems, which characterize this sleep stage (Steriade and Contreras 1995). Neocortical, thalamocortical, and thalamic reticular neurons are interconnected in networks that generate the 3 main EEG sleep rhythms: spindles, delta, and slow oscillation. The priming role of the neocortex in generating the slow oscillation that groups the other SWS rhythms (reviewed in Steriade 2003) as well as some

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**Figure 7.** Spatiotemporal characteristics of ictal events. (A) Propagation of paroxysmal activities on the cortical surface during wake and SWS in a chronic cat with a deafferented left suprasylvian gyrus in day 15 after the cortical undercut. The position of the recording electrodes is depicted on right scheme, and the undercut is represented as a gray box. Whereas during wake the ictal events appear consecutively in different EEG channels, during SWS they display a tendency toward a simultaneous occurrence. (B) Activities occurring in 4 EEG channels (anterior marginal left and right gyrus and posterior suprasylvian left and right gyrus) were correlated over 30 s and depicted as average correlations. (C) Average correlation time lag in 4 different chronic cats.
Figure 8. Intracellular correlates of seizures. (A) EEG in the marginal gyrus (EEG1) and local field (EEG2), EMG, EOG, and intracellular recording of a regular-spiking neuron in a chronically implanted, naturally awake and sleeping cat, with a cortical undercut over the left suprasylvian gyrus, 15 days after deafferentation. (B) Patterns of neuronal activity during SWS, REM, and wake. Note the presence of hyperpolarizing events during both wake and REM sleep (pointed by arrows) that are expressed as the minor peak in the histograms of membrane potential (C). (C) Histograms of membrane potential distribution during SWS, REM, and wake. (D) Duration of the hyperpolarizations in the intracellular recording, during SWS, REM, and wake. These hyperpolarizing events are grouped in 2 clusters: short-length (<100 ms) and long-length (around 200–300 ms), and their occurrence is modulated by the state of vigilance. (E) Changes in the pattern of discharge of cortical neurons during various states of vigilance. Peri-spike histograms indicate a predilection for bursting behavior during SWS and wake, whereas during REM sleep neurons display a tonic-firing pattern.
types of SW seizures (which may develop without discontinuity from the slow oscillation; see Introduction) is demonstrated by several data. The slow oscillation is generated in cortex even after extensive thalamic lesions (Steriade and others 1993) and was also recorded in cortical slices (Sanchez-Vives and McCormick 2000) and isolated cortical slabs (Timofeev and others 2000). On the other hand, SW seizures occur in neocortex of thalamectomized animals (Steriade and Contreras 1998), and thalamocortical neurons are steadily hyperpolarized during cortically elicited SW seizures, via excitation of thalamic reticular neurons that faithfully follow paroxysmal depolarizing shifts of cortical neurons (Steriade and Contreras 1995; reviewed in Crunelli and Leresche 2002).

Although SWS is the behavioral state during which these seizures occurred most often in the present study, which is in line with clinical studies (see Introduction), these seizures were also observed during wakefulness (Figs 2, 3, and 5), but the time lags of SW propagation were much longer in waking than in SWS. The seizures during waking may be related to the presence of hyperpolarizations after cortical deafferentation (Fig. 8), which stands in contrast with absence of such events during waking of nonepileptic cats (Steriade and others 2001). The waking-related hyperpolarizations detected in the present experiments on animals with cortical undercut could facilitate the expression of \( I_{h} \) and the Ca\(^{2+}\)-activated rebound depolarization is known to promote paroxysmal activity with SW patterns (Timofeev and others 2002).

One of the characteristics of the 3- to 4-Hz SW complexes occurring during waking state was their relationship with the eye movements. Indeed, the EOG displayed deflections at the beginning and/or at the end of the ictal events matching the important manifestations of eye movements in the clinical expression of absence epileptic seizures in humans, which range from minimal changes of fixation, or prolonged fixation (staring, centering), to a large variety of lateral or oblique concomitant nystagmoid jerks and, in some instances, tonic conjugate deviation (Bickford and Klass 1964). Beside clinical observations, there are only few studies dealing with ocular motility during absence seizures. The eye movements could reflect a propagation of the ictal discharge to the brainstem (Bogacz and others 2000) because a previous study demonstrated a marked dependence of saccadic parameters on global EEG oscillations (Skrandies and Anagnostou 1999).

In summary, our results support the conclusion that alterations in the intracortical synaptic network result in a significant shift of the balance between excitatory and inhibitory inputs on pyramidal neurons toward increased excitation. Both epileptogenesis and the propagation of seizures are modulated by the state of the cortical network. Highly synchronous activity in corticothalamic systems promotes epileptogenesis and seizures propagation during SWS sleep and waking following cortical deafferentation, whereas paroxysmal activities were obliterated during REM sleep. Epileptogenesis during waking and SWS was also supported by the presence of hyperpolarizing events at the level of the cortical neurons, favoring the occurrence of bursts in the activity pattern of the cortical neurons.

Notes
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References