Spike-Wave Complexes and Fast Components of Cortically Generated Seizures. II. Extra- and Intracellular Patterns

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Steriade, Mircea, Florin Amzica, Dag Neckelmann, and Igor Timofeev. Spike-wave complexes and fast components of cortically generated seizures. II. Extra- and intracellular patterns. J. Neurophysiol. 80: 1456–1479, 1998. In the preceding study, we have shown that bicuculline-induced SW seizures are abolished after decortication, whereas cortical SW seizures survive thalamectomy and, thus, do not depend on spindle oscillations. That study used extracellular recordings under barbiturate anesthesia. Here, we report the intracellular patterns of spontaneously occurring and electrically induced seizures consisting of SW or polyspike-wave (PSW) complexes at 1.5–3 Hz and fast runs at ~10–15 Hz. Several issues led us to explore this topic.

1) SW complexes at ~3 Hz build up primary generalized seizures in humans (reviewed in Gloor and Fariello 1988; Huguenard and Prince 1997) and, at faster frequencies (7–9 Hz), some models of absence epilepsy in rodents (Kandel et al. 1991; Ruta et al. 1991). The patterns of seizures investigated in the present series of studies included, in addition to typical SW/PSW complexes, fast runs of activity. This compound pattern is reminiscent of the electrographic features characterizing some forms of malignant epileptic encephalopathy in humans, such as the Lennox-Gastaut syndrome in which fast electroencephalogram (EEG) runs are intermingled with somewhat slower (1.5–2 Hz) SW complexes (Halasz 1991; Niedermeyer 1988, 1993; Yaqub 1993). The mixed patterns of SW complexes and fast runs of EEG activity are typical for such patients (Gastaut et al. 1966). Although this pattern is usually described as generalized (Dulac and N’Guyen 1993; Yaqub 1993), multifocal independent “spikes” and SW patterns have also been described in this sleep-activated syndrome (Burnstine et al. 1991; Kotagal 1995). And, although some have suggested that the Lennox-Gastaut syndrome has a brain stem origin (Yagi 1996), others have implicated intracortical neuronal networks because of focal disturbances of cortical metabolism (Miyauchi et al. 1988) and favorable outcome for overall seizure incidence after callosotomy (Reutens et al. 1993) or focal corticectomy (Burnstine et al. 1991). We do not assume that the present experimental studies may shed light on the etiology of such seizures; nonetheless, we will show that our intracellular and field potential recordings bear striking resemblances to EEG records in clinical seizures, and we postulate that the electrophysiological mechanisms of these cortically generated paroxysms, revealed in the present paper, are similar to those occurring in humans and behaving animals.

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light sleep in behaving monkeys (Steriade 1974) and humans (Kellaway 1985). Recent intracellular studies (Steriade and Amzica 1994; Steriade and Contreras 1995) have emphasized that SW seizures emerge without discontinuity from the slow (<1 Hz) sleep oscillation (Steriade et al. 1993a,b). In the present study, we compare the relations between cortical field potentials and intracellular activities during the slow oscillation and during SW/PSW paroxysms.

3) We also thought of interest to compare the seizure-related activities in regular-spiking (RS) and fast-rhythmic-bursting (FRB) cortical neurons. The former constitute the majority of neocortical cells and have been known since the early 1980s (reviewed in Gutnick and Mody 1995). The FRB cells, although representing a lower percentage, discharge high-frequency spike bursts at fast rates (Gray and McCormick 1996; Steriade 1997) and, thus, may exert powerful influences on cortical as well as thalamic neurons because some of them have been identified as projecting to various thalamic nuclei (Steriade et al. 1998). The present data suggest that FRB cells may contribute to play an important role in the initiation of SW/PSW seizures associated with runs of rapid activity.

4) Finally, the impaired cognitive processing during the SW complexes associated with the Lennox-Gastaut syndrome (Sengoku et al. 1990) led us to investigate cellular excitability during these seizures and to compare the data obtained during paroxysmal activity to those during pre- and postseizure epochs.

METH ODS

Experiments were conducted on 72 adult cats of either sex.

Chronically implanted animals

Spontaneously occurring seizures were recorded from three cats that were chronically implanted under ketamine anesthesia (15 mg/kg im) followed by barbiturate anesthesia (somnotol, 35 mg/kg ip). Bipolar coaxial electrodes were inserted into neocortical areas 4 (motor), 3 and 1 (somatosensory), 17 (primary visual), 22 (auditory), 5 and 7 (association), as well as in thalamic rostral intralaminar central lateral (CL), lateral posterior (LP), and dorsal part of lateral geniculate (LG) nuclei. A hole in the calvarium above the left suprasylvian gyrus (areas 5 and 7), which was sealed between recording sessions, allowed the placement of tungsten microelectrodes (impedance 3–8 MΩ) for extracellular recordings of unit activity and local field potentials. The electromyogram (EMG) from neck muscles and electrooculogram (EOG) were also recorded to assess the behavioral state of vigilance. Buprenorphine (0.03 mg/kg im) was given every 12 h for 24 h to prevent pain after surgery. The animals were allowed to recover for 2 wk. During recording sessions, the head of the cats was kept rigid without pain or pressure, as previously described (Steriade and Glenn 1982). During recording, the animals could move their limbs and often made postural adjustments.

Acute experiments

Sixty-nine cats were anesthetized with ketamine and xylazine (10–15 and 2–3 mg/kg, respectively). All tissues to be incised were infiltrated with lidocaine. The depth of anesthesia was monitored by continuous recording of the EEG. Supplementary doses of ketamine and xylazine (3–4 and 0.6–0.8 mg/kg, respectively) were administered at the slightest changes toward diminished amplitudes and increased frequencies of EEG waves. Heart rate (acceptable range 90–110 beats/min) and temperature (36–39°C) were monitored. When the EEG indicated that deep anesthesia was installed and the animal displayed sleeplike patterns, a muscle relaxant (galamine triethiodide) was administered, and the animal was mounted in a stereotactic frame and artificially ventilated under the control of end-tidal CO2 between 3.5 and 3.8%. To compensate for fluid loss, 20–30 ml iv saline were given during the experiments, which lasted 8–12 h.

RECORDINGS. 1) Field potential recordings were made with coaxial electrodes placed with the ring at the cortical surface and the tip at ~0.8–1 mm in the cortical depth of prerequisite cortical area 4 and suprasylvian areas 5, 7, and 21. Minor adjustments of depth were subsequently made, based on the pattern of the slow sleep oscillation so that the reversal of depth-to-surface signals was obtained (see Contreras and Steriade 1995). Coaxial recording electrodes were also inserted in the thalamic CL, LP, and ventral lateral (VL) nuclei. Field potentials were also recorded by means of tungsten microelectrodes (3–8 MΩ) inserted at different depths of various cortical areas. 2) Extracellular unit recordings were obtained through the same type of tungsten microelectrodes, in conjunction with focal slow waves. 3) Single or dual simultaneous intracellular recordings were obtained by means of glass microtipettes filled with 3 M potassium acetate (DC resistance, 25–45 MΩ). We recorded from motor area 4, association areas 5 and 7, and thalamic VL nucleus. The stability of intracellular recordings was ensured by the drainage of cisterna magna, hip suspension, bilateral pneumothorax, and by filling the hole made for recordings with a solution of 4% agar. A high-impedance dual amplifier (for dual intracellular recordings) with active bridge circuitry was used to record from, and inject current into, the neurons. The signals were band-pass filtered (0–9 kHz), digitized at 20 kHz, and stored on an eight-channel tape recorded for off-line analysis.

In addition to spontaneously occurring seizures, we induced paroxysmal activities by 1) using electrical stimulation of cortical areas or appropriate thalamic nuclei and 2) inserting in the rostral part of area 5 a syringe filled with 10 μl of a 0.2-mM solution of bicuculline in saline; bicuculline was not injected, but very small amounts (0.02–0.05 μl) slowly leaked into the cortex (see RESULTS).

At the end of experiments, the cats were given a lethal dose of intravenous pentobarbital sodium and perfused intracardially with physiological saline followed by 10% formaldehyde. The location of stimulating and recording electrodes was verified on 80-μm sections stained with thionine.

RESULTS

We present the results in the following order. First, we report data from chronically implanted animals on spontaneously occurring, mainly localized cortical seizures, consisting of SW complexes at 2–4 Hz or SW/PSW complexes associated with fast runs at 10–15 Hz or even higher (Figs. 1–3). Second, we present data from acutely prepared animals, using single or dual simultaneous intracellular recordings during spontaneous or electrically induced seizures of cortical neurons, consisting of SW/PSW complexes at 2–4 Hz and fast runs at 10–15 Hz. We start with spontaneous seizures recorded by means of intracellular recordings of two major types of neocortical neurons (RS and FRB), in conjunction with field potentials (Figs. 4–9). Next, we present electrically induced seizures (by stimulating the cortex or thalamus) using single or dual intracellular recordings from cortex or from cortex and related thalamic nuclei (Figs. 10–12). Further, we explore the intracellular excitability by...
FIG. 1. Spontaneously occurring cortical spike-wave (SW) seizure in chronically implanted animal. Five traces depict (from top to bottom): field potentials from the depth of somatosensory area 3; extracellular unit activities of 2 cells from association suprasylvian area 5 (1 and 2), each recorded simultaneously with focal slow waves through the same micropipette; field potentials from the depth of visual area 17; and electrooculogram (EOG). The seizure, consisting of SW complexes at 3 Hz, occurred within 2 sites in area 5. Part framed in the top panel is expanded below. Note close time relations between spike trains or spike bursts of cortical neurons and focal negative waves. In this and following figures, downward deflections of field potentials indicate negativity (as in intracellular recordings).

injecting depolarizing current pulses during the slow sleep-like oscillation and different epochs of seizures (Figs. 13–15). Finally, we show that the patterns of spontaneous seizures are basically similar to those elicited by diffusing small amounts of bicuculline into the cortex (Fig. 16).

Database and electrophysiological properties of recorded neurons

The results are based on analyses of spontaneously occurring seizures (n = 192) and electrically elicited seizures (n = 267). I) Of 192 analyzed spontaneous seizures, 43 occurred in chronic, and 149 in acute, experiments. In chronically implanted animals, we recorded 16 pure SW seizures (37%) and 27 compound seizures made of SW complexes and fast runs (63%). See below (section entitled SW and PSW cortical seizures in chronically implanted animals) the possible factors that may account for the occurrence of spontaneous seizures in behaving animals. In acutely prepared animals, 44 spontaneous seizures were purely SW or PSW complexes, and 105 were compound (SW/PSW and fast) seizures.
(30 and 70%, respectively). 2) Of 267 seizures triggered by electrical stimulation of cortex or thalamus in acute experiments, 110 (41%) consisted of pure SW/PSW complexes, whereas 157 (59%) were made of both SW/PSW complexes and fast runs.

We analyzed data obtained by using intracellular recordings during seizures from 384 cortical neurons. Of those, dual impalements were performed in 80 cell couples (160 neurons). Two major types of cortical neurons were analyzed in this study: RS (296/384, 77%) and FRB (23%). Although the patterns of slow- and fast-adapting RS cells have been known from earlier in vitro (Connors et al. 1982; McCormick et al. 1985) and in vivo (Nunez et al. 1993) studies, FRB neurons have been described in superficial layers of visual cortex (Gray and McCormick 1996) as well as in superficial and deep layers of motor and association areas (Steriade 1997; Steriade et al. 1998), where the present experiments have been conducted. FRB neurons are recognized by their responses to depolarizing current pulses, consisting of high-frequency (300–600 Hz) spike bursts recurring rhythmically at 20–40 Hz (see Fig. 7B).

SW and PSW cortical seizures in chronically implanted animals

The majority of spontaneous cortical SW seizures (29/43) occurred during the behavioral state of resting sleep, whereas the remaining paroxysms occurred during wakefulness. During resting sleep, the SW seizures were not accompanied by any motoric sign. None of them occurred during rapid-eye-movement (REM) sleep. When they appeared during wakefulness, phasic eye movements and increases in muscular tone were no longer observed throughout the seizures (Figs. 1 and 2). The occurrence of spontaneous cortical SW seizures in chronically implanted animals, first shown in behaving monkeys (Steriade 1974) and documented here in cats, is probably due to the great number of coaxial macroelectrodes and microelectrodes in various cortical areas and thalamic nuclei (see METHODS) that may have produced small lesions and gliosis, combined with the fact that we often applied stimuli to physiologically identify the input-output organization of cortical and thalamic neurons.

Figure 1 illustrates a typical, brief SW seizure at 3 Hz, occurring in two adjacent sites within the cortical suprasylvian area 5. The two extracellularly recorded neurons invariably discharged spike trains or spike bursts during the depth-negative “spike” EEG component and were silent during the depth-positive wave component of SW complexes. That SW seizures were localized within relatively circumscribed neocortical territories was shown by wave-triggered averages (WTA) and sequential cross-correlations of focal field potentials from multiple sites (see legend of Fig. 2 for methods used to calculate WTA and cross-correlations). At visual inspection, the 4-Hz SW seizure depicted in Fig. 2 was only visible in somatosensory area 3, but WTA and cross-correlations indicated related activities at ~4 Hz in adjacent area 1 as well as in association area 7. However, the motor (area 4), primary visual (area 17) and auditory (area 22) leads did not exhibit signs of paroxysmal activity.

Spontaneous seizures with the features described above occurred in two of three chronically implanted animals. The third one displayed more complex spontaneous seizures that, although initiated in distinct cortical foci, spread to both hemispheres and eventually included some thalamic nuclei. Such compound seizures consisted of SW or PSW complexes at 1.5–2 Hz and fast runs of waves. The paroxysm in Fig. 3 started during light sleep with fast waves (~10 Hz) over the left area 17 (asterisk in A), that developed into even faster waves (~30 Hz) over both areas 17 and 5 (asterisk in B), eventually leading to a full-blown cortical and thalamic seizure consisting of PSW complexes at 1.5–2 Hz (C). There was no clear-cut postictal depression at the EEG level (but see below in intracellular recordings, Fig. 4).

Intracellular patterns of spontaneous seizures in anesthetized animals

The majority (70%) of spontaneously occurring seizures recorded intracellularly were formed by SW or PSW complexes (generally at 2–3 Hz, occasionally at 1.5) and fast runs of activity (at 10–15 Hz). These two major components appeared in alternation (Fig. 4). The duration of these compound seizures ranged between 20 and 90 s (median, 33 s).

Most frequently (90 of 105 seizures), the seizures started with low-frequency (1–1.5 Hz), spiky EEG waves. Intracellularly, these events are termed paroxysmal depolarizing shifts (PDSs) and are sudden depolarizations that last for hundreds of milliseconds and trigger a series of action potentials (Ayala et al. 1973; Johnston and Brown 1981; Matsumoto and Ajmone-Marsan 1964). In the present experiments, the PDSs increased their frequency and became SW/PSW rhythmic complexes at 2–3 Hz, followed by a period with fast runs, to end at the lower frequencies observed at seizure onset. The remaining 15 seizures started with fast runs that were followed by SW/PSW complexes. In 95 of those 105 spontaneous compound seizures (90%), their onset gradually developed from the slow sleeplike oscillation (Fig. 4). The remaining few seizures (10%) occurred suddenly (see below, Fig. 6).

The common aspect, major components, duration, and evolution of seizures in intracellularly recorded cortical RS neurons are illustrated in Fig. 4. The seizure evolved without apparent discontinuity from the slow sleeplike oscillation at 0.9 Hz (1st 12–13 s of A) that was characterized by its alternating depolarizing (~67 mV) and hyperpolarizing (~80 mV) components. The first part of the seizure, lasting ~16 s, was formed by SW complexes at 2 Hz; it was followed by a period of ~2 s with fast runs at ~15 Hz; thereafter, SW complexes appeared again and decreased their frequency; and the seizure ended with a postictal depression of ~6 s. Clearly, the seizure was associated with a progressive depolarization, associated with partial spike inactivation (see the continuously rising spike threshold above the dotted line indicating the depolarizing component of the slow oscillation before seizure). The depolarization reached maximum value during the fast runs. This was a constant finding in the majority of analyzed neurons (see Figs. 4, 9, and 15).

The fact that compound seizures progressively evolved from sleep patterns was substantiated by analyses using
FIG. 2. Spontaneous, focal cortical SW seizure and its synchronization with adjacent, but not with distant, cortical areas. Chronically implanted animal. Eight traces in the top panel depict the following: field potentials from the depths of areas 4, 3, 1, 7, 17, and 22; EOG and electromyogram (EMG). Duration of seizure was ~15 s. Bottom left panel illustrates wave-triggered average (WTA) from seizure period between dotted lines in the above panel; reference time is represented by peak negativities (dotted line) in area 3 where SW complexes at 4 Hz were prominent. Note that SW complexes in area 3 were reflected by lower-amplitude, clear-cut waves at the same frequencies in areas 1 and 7, but not in areas 4, 17, and 22. The WTAs were calculated as follows: negative peaks for each electroencephalogram (EEG) spike in area 3 were detected, and equal windows around that point (1 s before and 1 s after) were extracted from all channels. All sweeps belonging to a given channel were finally averaged. Bottom right panel depicts a perspective view of a 3-dimensional sequence of cross-correlations (CROSS) between activities in the primary focus of SW seizure (area 3) and the adjacent area 1. The same windows as for WTA also served to generate sequential field correlations (see method in Amzica and Steriade 1995). Briefly, the 3-dimensional surface was derived as follows: each couple of sweeps from 2 EEG leads (e.g., area 3 and area 1) corresponding to a given EEG spike was cross-correlated, thus producing a correlation trace. Then, all correlation traces were sequentially aligned to produce a 3-dimensional surface in which the abscissa (−0.5–0.5 s) corresponds to the time lags; each point of the ordinate is a time mark for an EEG spike; and the z-axis represents the strength of the correlation. The shadows on the 3-dimensional surface attribute white to high positive correlations, and black to high, but negative correlation.

The WTA of intracellular and field potential activities. Figure 4B was based on averaged activities triggered by the steepest slope of the depolarizing onset in area 5 neuron, and shows 1) the close time relation between the depolarizing component of the slow sleeplike oscillation and the depth-negative cortical field potential, representing the EEG K-complex (see DISCUSSION); and 2) the increased amplitude of the depolarizing component of slow oscillation, reaching the level of PDSs during seizure, as well as the increased frequencies of these paroxysmal events to become SW complexes at ~2–3 Hz.

Thus the patterns of SW seizures were an exaggeration of depolarizing and hyperpolarizing components of sleep patterns (deriving from the sleep K-complex), while keeping similar relations between intracellular activities and EEG components. However, despite these apparent similarities between sleep and paroxysmal events, the seizures illustrated in Figs. 4 and 5 were basically distinct from pre- and postseizure epochs by a series of neuronal characteristics, as follows. 1) The progressive depolarization reached a maximum during the fast runs when action potentials were partially inactivated. This progressive depolarizing envelope was not visible in all seizures (see Figs. 6–8, and DISCUSSION). 2) The depolarizing envelope evolved simultaneously with an increased hyperpolarization (note, in Fig. 4, the evolution of $V_n$, above and below dotted lines at −67 and −80 mV, respectively). By contrast, such events did not occur during the sleeplike slow oscillation. And, 3) a sudden arrest, with
FIG. 3. Spontaneously occurring, generalized seizure consisting of fast components at 10–30 Hz and polyspike-waves (PSW) at 1.5–2 Hz. Six EEG traces depict from top to bottom: field potentials in the right cortex (depths in areas 4 and 17) and right rostral intralaminar central lateral (CL) nucleus; and depth field potentials from left areas 4, 17, and 5. Besides, EOG and EMG were recorded. Epochs framed in the top panel (A, the beginning of seizure; B, epoch with fast components; and C, epoch with PSW complexes) are expanded below. Asterisk in A marks fast components at $\leq 10$ Hz. Asterisk in B marks fast components at $\leq 30$ Hz.

a postictal depression, was associated with a long-lasting hyperpolarization.

We measured the depolarizing and hyperpolarizing envelopes during seizures, at different $V_m$ levels ($n = 12$). Figure 5 depicts one of those neurons involved in unusually long seizures (80–90 s) to allow observation of tonic depolarizing-hyperpolarizing events throughout the seizure, during both resting and hyperpolarized (DC $–0.6$ nA) conditions. The evolution of activity in this area 5 neuron during the preseizure (sleeplike) and seizure epochs is shown in the gray panels. The three reference (dotted) lines represent the levels of depolarizing and hyperpolarizing components of the sleep oscillation as well as the extreme depolarization during the fast runs of seizures. Several points emerged from
FIG. 4. Spontaneously occurring seizure, developing without discontinuity from slow sleeplike oscillation. Intracellular recording from regular-spiking area 5 neuron together with depth-EEG from the vicinity in area 5. This and all following intracellular recordings are from cats under ketamine-xylazine anesthesia. A: smooth transition from slow oscillation to complex seizure consisting of SW complexes at \( \sim 2 \) Hz and fast runs at \( \sim 15 \) Hz. The seizure lasted for \( \sim 25 \) s. Epochs of slow oscillation preceding the seizure, SW complexes, and fast runs are indicated and expanded below. Note postictal depression (hyperpolarization) in the intracellularly recorded neuron (\( \sim 6 \) s), associated with suppression of EEG slow oscillation (compare to left part of trace). B: WTA during the slow oscillation, at the beginning of seizure and during the middle part of seizure. Averaged activity was triggered by the steepest part of the depolarizing component in cortical neuron (dotted lines), during the 3 epochs. The depth-negative field component of the slow oscillation (associated with cell’s depolarization) is termed K-complex (see DISCUSSION). During the seizure, the depolarizing component reaches the level of a paroxysmal depolarizing shift (PDS), associated with an EEG spike.
FIG. 5. Depolarizing and hyperpolarizing envelopes during spontaneously occurring cortical seizures. Intracellular and depth-EEG recording in area 5. Two panels (A, resting $V_m$; and B, under steady hyperpolarizing current) illustrate 2 different seizures in the same neuron (seizure in A lasted ~90 s, in B ~80 s). Below the EEG and intracellular trace, gray panels represent traces with respect to 3 $V_m$ levels: during the depolarization of the slow oscillation ($-61 \text{ mV in } A$, $-73 \text{ mV in } B$); during the hyperpolarizing phase of the slow oscillation ($-75 \text{ mV in } A$, $-89 \text{ mV in } B$); and during seizure depolarization ($-44 \text{ mV in } A$ and $B$). In both A and B, epochs 1 and 2 depict slow oscillations and seizures, respectively, and are expanded below. Note dramatic increase in depolarizing envelope during seizure; see text.
FIG. 6. Spontaneous seizure in regular-spiking cell from area 4. Intracellular recording together with depth-EEG from
the same precruciate area. The seizure lasted for ~22 s (indicated by arrows below the EEG trace) and was followed by a
period of postictal depression (hyperpolarization) lasting for ~3.5 s. The 2 major components of the seizure (fast runs at
~10 Hz and PSW complexes at ~2.5–3 Hz) are indicated by horizontal bars below the intracellular trace and arrows.

these analyses: 1) there were constant levels of depolarizing
and hyperpolarizing components during the slow oscillation
before seizure (see the 1st ~5–10 s at the extreme left of traces); 2) a progressive depolarization appeared in advance
of overt EEG signs of seizure, and this sign was more marked
at the hyperpolarized level; the precursor sign of depolariza-
tion occurred in 9 of 12 analyzed neurons; 3) during full-
blown seizures with fast components (panels 2), the plateau
of depolarization reached values more positive by 17 mV
(at rest) and 29 mV (~0.6 nA), compared with the levels
seen during the preseizure epochs, and was often associated
with complete spike inactivation; and 4) at rest, a hyperpo-
larizing envelope (~5–6 mV) accompanied the entire sei-
zure (see also Fig. 4) and was reduced by hyperpolarization
(Fig. 5).

The major differences between the two neuronal classes
analyzed in this study, RS (n = 296) and FRB (n = 88)
cells, are depicted in Figs. 6 and 7, respectively. The EEG
seizures (between horizontal arrows), consisted of PSW
complexes at 2–3 Hz and fast runs at 10–12 Hz and lasted
for 22 and 26 s. In essence, the RS neuron from area 4
discharged single action potentials or spike-doublets during
either depth-negative fast EEG runs or polyspikes of PSW
complexes (Fig. 6), whereas the FRB neuron from area
7 discharged spike bursts consisting of up to seven action
potentials during the depolarizing component of fast runs as
well as during each of the multiple EEG spikes composing
the PSW complexes (Fig. 7). These different firing patterns
are not attributable to the location of neurons in various
areas because they were also observed within the same area.

In 37% of spontaneously occurring seizures, the EEG ex-
hibited very fast ripples (120–140 Hz) during the excitatory
component of PSW complexes. The ripples appeared super-
imposed on the depth-negative envelope of polyspikes and
were made clear by filtering the trace to 80–300 Hz and by
adequate amplification. In fact, as shown in Fig. 8, such
very fast ripples also appeared, with reduced amplitudes
compared with seizures, during the depth-negative (depolar-
izing) field component of the slow oscillation (left arrow in
Fig. 8; see also inset in Fig. 14A). Intracellular recordings
of FRB cells during fast ripples (n = 15) demonstrated that,
on one hand, their propensity toward fast rhythmic spike
bursting was enhanced during ripples associated with the
slow sleep oscillation, and, on the other hand, the action
FIG. 7. Fast-rhythmic-bursting (FRB) cortical neuron during SW and fast seizure developing spontaneously from slow sleep oscillation. A: intracellular and depth-EEG recording from area 7. Seizure is indicated by arrows (below the EEG trace) and lasted for ~26 s. B: electrophysiological identification by depolarizing current pulse (0.2 s). See text. Epochs C and D in A are expanded below. C: slow oscillation before the seizure. D: both fast runs (~12 Hz) and PSW complexes (~2 Hz). Note high-frequency spike bursts in neuron during each depth negativity of fast EEG runs (compare with single action potentials in regular-spiking cell, Fig. 6).
FIG. 8. Fast ripples (120 Hz) during spontaneous cortical seizure. Intracellular and EEG recording from area 4. FRB neuron (identified as in Fig. 7B). The 2nd trace in the top panel is EEG filtered for fast events (80–300 Hz) and amplified. Two horizontal bars (below the intracellular trace) indicate the slow sleep oscillation (left) and the seizure (right), and are expanded below (arrows). One cycle of the PSW seizure is further expanded below (arrow). Note close time relation between the action potentials and EEG ripples. See also Fig. 14A.
Fig. 9. Depth profile of EEG events associated with seizure in intracellularly recorded neuron from area 5. Simultaneous recording of neuron (top trace) and field potentials from the surface and depths of 0.5, 1, and 1.5 mm. Seizure lasted for 50 s. Two epochs during the seizure, depicting PSW complexes at ~2 Hz and fast runs at ~11 Hz, are expanded below. Note progressively increased amplitudes of seizure field components from 0.5 to 1.5 mm, and their reversal at the surface. Note similar frequencies of fast runs (~11 Hz) and polyspikes in PSW complexes (~2 Hz). Multisite recordings showed that such fast ripples (~150 Hz) are synchronized over distances of at least 3 mm (not shown). Similar or even higher-frequency ripples, as well as association between field potentials and extracellular unit firing, have been described in the normal rat hippocampus (Buzsáki et al. 1983; Traub et al. 1985), where they may arise from electrotonic coupling of neurons independent from chemical synaptic transmission (Draguhn et al. 1998) and in rat neocortex during SW patterns (Kandel and Buzsáki 1997).

Last, in some instances (n = 7), we analyzed the depth profile of field potentials during spontaneously occurring PSW and fast seizures in conjunction with an intracellular recording from an adjacent site in the same suprasylvian area 5 or 7 (Fig. 9). Without exception, the rhythmic PSW complexes at ~2 Hz and fast runs at 10–15 Hz, associated with paroxysmal
depolarizing events in the intracellularly recorded neurons, were reversed more superficially than 0.3 mm.

Intracellular patterns of electrically induced seizures

We were able to reproduce the basic patterns of spontaneous seizures (with SW or PSW complexes and fast runs) by electrically stimulating cortical areas 4 and 5–7 or dorsal thalamic (VL, CL, and LP) nuclei (n = 267) while recording intracellularly from single cortical, pairs of cortical, or pairs of cortical and thalamic neurons.

Dual simultaneous recordings from cortical areas 5 and 7 during a seizure elicited by cortical stimulation showed a twofold increase of the paroxysmal depolarization during SW complexes at 2–4 Hz, as compared with the amplitude of the depolarizing component during the slow oscillation that preceded and succeeded the seizure (Fig. 10). About 40% of simultaneously recorded thalamic neurons from appropriate nuclei reflected the cortical seizures by firing rebound spike bursts related to the bursts of cortical cells (see, for example, the extracellular recording of CL neuron in Fig. 10). However, the majority of dorsal thalamic neurons did not participate actively in the seizure. Instead, they exhibited a diminished discharge rate compared with pre- and postseizure epochs. This aspect is illustrated in Fig. 11, depicting a dual simultaneous intracellular recording from area 4 and thalamic VL neurons. Stimulation of cortical area 4 with a pulse train at 10 Hz (horizontal bar; arrow marks the expanded responses) induced a self-sustained seizure in cortex, consisting of SW and PSW complexes at 3 Hz and lasting ~10 s. Simultaneously to the clear-cut seizure in the cortical neuron, the VL cell displayed decreased firing rate during the seizure as well as during the stimulation period.

The basic components of cortical seizures were also elicited by thalamic stimulation with pulse trains at 7–10 Hz. In Fig. 12, the seizure in area 5 was long lasting (~40 s) and consisted of I) PSW complexes (B1), during which the action potentials in the area 5 neuron were fired syn-
FIG. 11. Different activity patterns in cortical and thalamic neurons during cortically elicited seizure. Dual intracellular recordings from area 4 and thalamic ventral lateral (VL) neurons, simultaneously with depth-EEG from area 4. Cortical stimulation at 10 Hz (see horizontal bar below VL neuron) triggered a seizure with SW and PSW complexes at 3 Hz (see bottom right panel). During stimulation as well as during SW seizure, VL neuronal discharges diminished in comparison with preseizure and postseizure epochs. Note postictal depression (hyperpolarization) in area 4 neuron (lasting for ~8 s), despite the fact that EEG from the vicinity did not show similar depression.

chronously with the negative field potentials in cortex and thalamus; and 2) fast runs (B2), having the same frequency as the polyspikes of PSW complexes, during which the cortical neuron fired spike doublets. Note that, although at a gross visual inspection the depth-EEG from area 7 did not display overt signs of seizures, the expanded traces (B1 and B2) show its activity as fully synchronized to that of the prevalent focus in area 5.
FIG. 12. Thalamically elicited seizure. A: 4 traces depict (from top to bottom): depth-EEG from area 5, intracellular recording of area 5 neuron, depth-EEG from area 7, and electrothalamogram (EThG) from lateral posterior (LP) nucleus. Thalamic stimulation, applied to CL nucleus, consisted of pulse trains (2, 3-ms delayed shocks) repeated at 7 Hz. Stimulation elicited a seizure that lasted for ~40 s and consisted of PSW complexes at ~1.5 Hz and fast runs at ~13 Hz. Two epochs from A, representing PSW complexes and fast components, are expanded in B1 and B2, respectively. Period marked by asterisk in B1 is expanded at right (depth-EEG, intracellular trace, and EThG are illustrated, filtered and amplified) to show the close time relations, during the polyspikes of PSW complexes, between action potentials and cortical as well as thalamic field potentials. Period marked by 2 asterisks in B2 is expanded at right to show spike doublets during fast runs.
Cellular excitability during cortical seizures

Neuronal excitability was tested in RS \((n = 18)\) and FRB \((n = 7)\) cortical neurons by means of depolarizing current pulses \((0.2–0.3 \text{ s}, 0.5–0.8 \text{ nA})\) applied before, during, and after electrically induced or spontaneously occurring seizures.

During the slow oscillation of slowly adapting RS neurons, depolarizing current pulses elicited spike trains. The number of evoked action potentials generally decreased during the SW complexes of the cortically elicited seizure, became virtually zero during the postictal depression, and then progressively recovered to reach control values when the slow oscillation reappeared (Fig. 13). Alterations in discharge patterns elicited by direct depolarization were also observed by testing FRB cells (Fig. 14). Their typical high-frequency \((300–600 \text{ Hz})\), rhythmic \((20–40 \text{ Hz})\) spike bursts occurred during the slow oscillation, and the initial few seconds of seizures with SW/PSW complexes evolving insidiously from the slow oscillation, but degenerated during the full-blown seizure. Thus the regularly
FIG. 14. Dynamic changes in excitability of FRB cortical neuron during slow oscillation and PSW seizure at 2 Hz. Intracellular recording of FRB neuron from area 7 (identified as in Fig. 6B), together with depth-EEG from areas 5 and 21. The onset of seizure is indicated by arrow (below the top EEG trace). Depolarizing current pulses (0.5 nA, 0.3 s) were applied at a rate of 1 Hz. Before seizure, during the slow oscillation, the neuron discharged high-frequency (400 Hz) spike bursts recurring rhythmically at ~25 Hz. This pattern also occurred at the beginning of PSW seizure (see the 1st depolarizing current pulse in A, ~4 s after seizure onset). Later on, however, the responses to depolarizing current pulses degenerated to single spikes or spike doublet (2nd depolarizing current pulse in A) and to a single spike burst followed by single spikes or spike doublets (B). Asterisks in A point to fast ripples (~120–140 Hz) during the depth negativity of PSW complexes; one of these epochs is expanded at right (see also Fig. 8). Note that depth-EEG from areas 5 and 21 showed larger synchrony during the full-blown PSW seizure at 2 Hz (with area 5 preceding, in B) than what was observed during the early period of seizure (A).
FIG. 15. Protracted, rhythmic, direct depolarization of FRB cell preceded appearance of full-blown seizure in the neighboring network, consisting of PSW complexes at 2 Hz and fast runs at 12–13 Hz. Four traces in top panel depict, from top to bottom, depth-EEG from area 5, intracellular recording of FRB neuron from area 5 (identified by 0.5-s depolarizing current pulses; see Figs. 7B and 14A), depth-EEG from area 7, and EthG from LP nucleus. The intracellular trace starts with a period lasting for 33 s during which depolarizing current pulses (30 ms, 0.8 nA) were delivered to the cell at a rate of 10 Hz. Panel 1 depicts below the responses to depolarizing current pulses. Ten seconds before pulses were no longer applied, the area 5 depth-EEG recorded close to the cell displayed the onset of a PSW seizure at 2 Hz. Panel 2 depicts the pattern of seizure, during which the EEG PSW complexes were sometimes associated with action potentials in the intracellularly recorded neuron. Panels 3 and 4 depict epochs with fast runs. Note, in 4, during an interrupted period of fast runs, spike bursts of the FRB neurons during each depth-negative field potentials of fast activity (similar to the FRB cell in Fig. 7D and dissimilar to the single action potentials in RS cell in Fig. 6). Also note reflection of fast runs in directly connected area 7 and thalamic LP nucleus.
recurring 8 to 10 spike bursts of FRB cells, elicited by a 0.3-s depolarizing pulse during the slow oscillation, deteriorated toward the end of the pulse during the first seconds of the seizure as well as during later periods of the seizure (Fig. 14, A and B). As a rule, when SW/PSW seizures were fully developed (Fig. 14B), current pulses applied during the depth-positive ("wave") component of PSW complexes triggered one or two high-frequency spike bursts, whereas during the depth-negative ("spike") component, associated with strong synaptic excitation, the depolarizing pulse triggered single spikes or spike trains.

FIG. 16. Patterns of bicuculline-induced cortical seizures, consisting of SW/PSW complexes at ~2–2.5 Hz and fast runs at ~9–10 Hz, are similar to those occurring spontaneously. A microsyringe with bicuculline was inserted in the anterior part of area 5 (focus in the top brain figure), whereas intracellular and field potential recordings were performed from more posterior regions in the same area (see figure). Bicuculline was not injected but diffused from the syringe (see text). A full-blown seizure is depicted in the top panel, with fast runs and PSW complexes in A, and PSW complexes and fast runs in B (expanded below).
Because of the high-frequency, fast repetitive spike bursts that characterize FRB neurons (Steriade et al. 1998), we hypothesized that, if rhythmically stimulated, their impact on local networks could be enough to initiate seizures focally and in related structures. In four animals, protracted (30–60 s) series of repetitive (10 Hz) depolarizing current pulses indeed resulted in seizures. In those cases, the seizures were the first to appear during the course of experiments. Seizures were not observed when depolarizing current pulses were delivered, with the same parameters, in RS cells (: n = 16). Figure 15 shows that, after prolonged (50 s) direct stimulation of an FRB neuron in area 5, a seizure consisting of PSW complexes at 2 Hz and fast runs at 12–13 Hz appeared not only in the stimulated neuron but also in the focal EEG recorded in the same area as well as in related area 7 and thalamic LP nucleus (see panel 4).

**Paroxysms similar to spontaneously occurring or electrically induced seizures are induced by small amounts of bicuculline leaked into the neocortex**

In 29 of 69 acutely prepared cats, a microsyringe filled with bicuculline was inserted into the most rostral part of the suprasylvian gyrus (area 5a). In the present study, bicuculline was not injected to obtain seizures, but very small amounts (0.02–0.05 μl of a 0.2-mM solution) diffused undesirably in the cortex. This was inferred because seizures predictably appeared after about a half hour in the adjacent area 5b whereas, by filling the microsyringe with saline, such paroxysms did not appear in close time relation with the insertion of the syringe. Although the seizures that followed the diffusion of bicuculline had a much longer latency (~25–40 min) and shorter duration than after deliberate injection of this γ-aminobutyric acid-A (GABA_A) antagonist (seizure latencies of 2–3 min), the seizure patterns were similar in both cases, and they also resembled those described above as occurring spontaneously or after electrical stimulation of the cortex and thalamus. Data from injections of bicuculline are reported in the following paper (Neckelmann et al. 1998). Briefly, the seizures (up to 3 min, compared with the 20–90 s in the case of spontaneous seizures) consisted of SW or PSW complexes at 2–2.5 Hz, alternating with fast runs at ~10 Hz (Fig. 16). Similarly to spontaneous seizures, the neurons were tonically depolarized during the fast runs, whereas they displayed rhythmic hyperpolarizations during SW/PSW complexes. The depth profile of field potentials in conjunction with the intracelluar recording (Fig. 16) was also similar to that observed during spontaneous seizures.

**Discussion**

We have shown that 1) spontaneous seizures with SW/PSW complexes and fast runs appear in behaving cats and are initiated in circumscribed cortical regions, but may eventually spread to related cortical areas and thalamic nuclei; 2) during spontaneously occurring seizures, intracellularly recorded RS neurons discharge spike trains during the EEG spike component, are hyperpolarized during the wave component, and undergo a tonic depolarization (sometimes leading to spike inactivation) during the fast runs; 3) FRB cells discharge many more action potentials than RS cells and, during fast runs, fire repetitive spike bursts; 4) similar relations between field potentials and intracellular activities are present both during slow oscillation preceding the seizure and throughout seizures, the latter being an exaggeration of the former; and 5) a diminished number of action potentials are elicited by depolarizing current pulses during SW/PSW complexes and fast runs of seizures, compared with prior periods of slow oscillation, and no responses are evoked during the postictal hyperpolarization.

**Seizures emerge without discontinuity from the cortical slow sleep oscillation**

In behaving cats, spontaneous SW seizures occurred during quiet waking, drowsiness, or resting sleep with low-frequency EEG waves, but not during REM sleep. The predominant occurrence of SW seizures during slow-wave sleep and their lowest incidence in REM sleep have also been reported in children with absence epilepsy (Sato et al. 1973). Patients with Lennox-Gastaut syndrome similarly display higher incidence of seizures during resting sleep than during wakefulness and REM sleep (Velasco et al. 1995).

In acutely prepared cats, most spontaneously occurring seizures, consisting of SW/PSW complexes and fast runs, emerged from the slow oscillation (95/105, 90%), with virtually no discontinuity (see Figs. 4–8). Analyses of averaged activities during seizures demonstrated similar relations between intracellular activities and field potentials as during the prior periods of slow oscillation. Thus it is reasonable to assume that the neuronal circuits used by the slow oscillation are basically the same as those mediating the paroxysmal discharges. This idea also resulted from previous experiments in which the self-sustained responses during the paroxysmal afterdischarge were nearly identical to responses evoked in the final stage of rhythmic stimulation (Steriade 1964). The slow neocortical oscillation, initially described under different types of anesthetics (Amzica and Steriade 1995; Contreras and Steriade 1995; Steriade et al. 1993a,b), appears with the same characteristics and frequency (mainly 0.7–0.8 Hz) during natural sleep of behaving cats (Amzica and Steriade 1998; Steriade et al. 1996) as well as during slow-wave sleep of humans (Achermann and Borbély 1997; Amzica and Steriade 1997). In particular, the sleep K-complex, represented by the depth-negative (surface-positive) cortical field potential associated with abrupt depolarizations of cortical neurons (Amzica and Steriade 1997, 1998), develops into the spiky excitatory component of SW/PSW complexes during seizures (see Fig. 4B). Both the slow sleep oscillation and the type of seizures described in this study are generated in neocortex. The cortical origin of the slow sleep oscillation was demonstrated by its presence in the cortex of thalamectomized animals (Steriade et al. 1993b), its absence in the thalamus of decorticated animals (Timofeev and Steriade 1996), and the disruption of its synchronization after disconnection of intracortical synaptic linkages (Amzica and Steriade 1995). The evidence for the cortical origin of seizures with SW/PSW complexes and...
fast runs is, on one hand, their disappearance after decortica-
tion and their survival after thalamectomy (Steriade and
Conterras 1998) and, on the other, the presence of similar
seizures in isolated cortical slabs (Timofeev et al. 1997,
1998). During cortical SW seizures, a majority of neurons
recorded from dorsal thalamic nuclei are steadily hyperpolar-
ized (Steriade and Conterras 1995) and diminish their firing
rates (see Fig. 11).

One may be surprised by the high incidence of SW/PSW
seizures that occurred spontaneously in both chronically im-
planted and acutely prepared cats under ketamine-xylazine
anesthesia. The high number of inserted electrodes that were
used in the present series of experiments and the fact that
we repeatedly used electrical stimulation for neuronal identi-
fication may represent a factor accounting for the incidence
of spontaneously occurring seizures. We also consider the
possibility that many spontaneous electrographic seizures in
‘normal’ subjects are unrecognized, and that those sleeping
individuals pass in and out of seizures during their slow
sleep oscillation, as we showed here for cats.

Two major components of cortically generated seizures
and their possible mechanisms

The definition of seizure is dealt with in the preceding
paper, together with the sharp distinction between cortically
generated seizures and the slowed spindles induced by bicus-
culline injection in the thalamus (see Steriade and Conterras
1998). In the present paper, SW complexes at 2–3 Hz were
associated with cellular events (depolarization and brisk dis-
charges during the EEG spike, hyperpolarization and si-
lenced firing during the wave component) that have also
been reported in other experimental models of SW seizures.
The other component of seizures, fast runs at 10–15 Hz,
displayed the same frequency range as the polyspikes of
PSW complexes. This was observed not only with intracellu-
lar recordings under ketamine-xylazine anesthesia (best seen
in Figs. 7D and 12, B1 and B2) but also during spontaneous
seizures in behaving animals (Fig. 3, B and C), and together
suggest common underlying mechanisms. Generally, the sei-
zures started with fast runs when they were elicited by elec-
trical stimulation. As to the postictal depolarization, it is not
usually reported after SW seizures, but, despite the fact that
EEG does not invariably show clear flattening, intracellular
recordings demonstrate long-lasting hyperpolarizations
(Figs. 4, 6, and 11) during which the cell’s excitability is
much reduced (Fig. 13). The postictal depolarization may pre-
vent the repetition of paroxysms with a higher incidence.

What are the factors that may account for the smooth
transition from sleep to seizure patterns? To begin with, it
should be emphasized that similar types of seizures (with
SW/PSW complexes at 2–3 Hz and fast runs at 10–15
Hz) occurred, spontaneously or after electrical stimulation,
under a variety of experimental conditions, such as behav-
ioral states of quiet waking or light sleep in unanesthetized
animals; ketamine-xylazine anesthesia; and the same seizure
patterns were precipitated by bicuculline infusion in the cor-
tex (see Fig. 16). Thus several nonexclusive mechanisms
can be invoked as contributing to the generation of these
cortically generated seizures.

Although the anesthesia used in the present study can-
ot alone be responsible for the major components building
up the seizures, because the same aspects occurred with
cortical injections of bicuculline under barbiturate anesthesia
(Steriade and Conterras 1998) and similar seizures were
reported here in unanesthetized animals (Figs. 1–3), we
briefly discuss the actions of ketamine. This antagonist of
N-methyl-D-aspartate (NMDA) receptors (Thomson 1986)
is considered among the most effective pharmacological
tools to enhance the synchronization processes underlying
slow-wave sleep (Feinberg and Campbell 1993). The syn-
chronizing effect of ketamine may be related to that of acti-
vating SW seizures in the feline penicillin model (Black et
al. 1980) and enhancing the primary and projected activity
resulting from chronic cobalt cortical foci (DeVore et al.
1976). However, other studies have reported the blockade
of cortical ictal events and anticonvulsive protection by ad-
ministration of a series of NMDA antagonists, among them
ketamine (e.g., Chen et al. 1996; Clifford et al. 1990; Hoff-
man et al. 1994). As mentioned above, ketamine was not the
only experimental condition under which seizures occurred.
Moreover, in view of the presence of such seizures during an
anesthesia that included ketamine, it is probable that the
development of hypersynchronized excitation within intra-
cortical circuits was mainly mediated by non-NMDA recep-
tors. In other structures (hippocampus), the depolarizing
events may implicate NMDA receptors, perhaps also depo-
larizing GABA_B-mediated events or metabotropic receptors
(reviewed in Traub et al. 1996).

2) We now discuss the contribution of different cell types
in the genesis and propagation of excitatory impulses during
seizures. The progressive depolarization during the seizure
eventually leads to a depolarizing plateau, with a ‘‘clamped’’
membrane, during which action potentials are partially or
totally inactivated (Figs. 4 and 5), and only inhibitory post-
synaptic potentials (IPSPs) are elicitable by thalamocortical
volleys (see Fig. 5 in Steriade and Amzica 1994). Many
neurons remain, however, capable of firing action potentials
during the depolarizing plateau (see Figs. 4 and 6–9), which
explains that the excitatory circuits are maintained. The fact
that the progressive depolarization and the plateau with spike
inactivation were more pronounced in some instances (Figs.
4 and 5) than in others (Fig. 6) might be explained by the
closer vicinity of the primary focus in the former cases.

Both the precursor signs of depolarization before any overt
paroxysmal signs are detectable in EEG recordings (Fig. 5),
and the depolarizing envelope throughout the seizure are
ascribed to the progressive entainment of excitatory circuits
through sequentially distributed synaptic linkages. This idea
is based on multisite recordings showing a progressive short-
eening in time lags, during seizure, between discharges of
simultaneously recorded neurons (Steriade and Amzica
1994). The propagation across neocortex is mediated by short-
and long-scale linkages, with particular types of neu-
rons playing a prevalent role in driving their targets and
entaining them into the seizure. Among these neuronal
types, intrinsically bursting (IB) cells from layers IV and V
have been hypothesized to play a role in the propagation
of bicuculline-induced synchronous events in cortical slices
(Chagnac-Amitai and Connors 1989). On direct depolariza-
tion, IB cells usually fire spike bursts up to 10 Hz (Núñez et al. 1993), and, in response to synaptic inputs during thalamocortical spindles, they do not follow frequencies higher than 4–6 Hz (see Fig. 7 in Steriade et al. 1993b). Thus these neurons would hardly follow the fast components (10–15 Hz) of the presently described seizures. By contrast, FRB neurons discharged spike bursts during each component of fast paroxysmal oscillation (Figs. 7 and 15). If interconnected, these neurons could have a great impact on cortical networks, especially during the fast components of seizures. It is interesting to note that the highest propensity toward SW seizures in behaving monkeys was found in cortical neurons displaying high-frequency spike bursts (see Figs. 5 and 6 in Steriade 1974). Those neurons were thought to be local-circuit cells, but the presence of FRB neurons was not known at that time.

We emphasize that the fast rhythmic spike bursts are not invariant patterns of FRB neurons because, as demonstrated in motor and association cortices, by further increasing the strength of the depolarizing current pulse, the rhythmic spike bursts coalesce and become tonic firing at 300–600 Hz without frequency adaptation (Steriade 1997). Furthermore, synaptic activities in thalamocortical and intracortical networks alter the pattern of rhythmic spike bursts (Steriade et al. 1998). This network effect on intrinsically generated fast rhythmic spike bursts of FRB cells was also observed by comparing inter spindle lulls with poor or null synaptic activity with periods associated with spindles in thalamocortical networks (Steriade et al. 1998). The present Fig. 14 also shows that the typical patterns of FRB cells, as tested during control periods of slow oscillation, are altered during periods with exceedingly high synaptic activity, as in seizures with PSW complexes. Surprisingly, virtually all FRB neurons, including those identified as corticothalamic by antidromic invasion from appropriate thalamic nuclei, have thin spikes, 0.3–0.4 ms at half-amplitude (Steriade 1997). As known, both the thin spike feature and the fast tonic firing without frequency adaptation that long axoned FRB neurons display by increasing the depolarization strength have conventionally been regarded as characterizing local-circuit inhibitory neurons (reviewed in Gutnick and Mody 1995). These considerations led to the conclusion (Steriade et al. 1998) that the distinctions between intrinsic electrophysiological properties of neocortical neurons are much more labile than previously thought.

As for the isolated or grouped PDSs, which may open the scene of full-blown seizures, they constitute giant, compound excitatory postsynaptic potentials (Johnston and Brown 1981, 1984) that depend on both network-driven synaptic potentials and peculiar membrane properties of various neuronal types having a high propensity to bursting. Layer V pyramidal neurons of the epileptic mutant mouse *stargazer* that shows SW seizures (Noebels et al. 1990) display a functionally autonomous hyperexcitability defect, partly due to a hyperpolarization-activated, cesium-sensitive inward current (DiPasquale et al. 1997).

3) Disinhibition is an additional factor for the generation of cortical seizures. Indeed, small amounts of bicuculline leaked into cortex gave rise to seizures with the same two major components as spontaneously occurring and electrically induced paroxysms (see Fig. 16). Both cortical and thalamic inputs produce IPSPs in pyramid neurons, mediated by local GABAergic neurons. Recordings with Cl\(^{-}\)-filled pipettes showed that thalamocortical spindle waves during barbiturate anesthesia are associated with powerful inhibitory processes in local cortical circuits that are transformed, after Cl\(^{-}\) intracellular diffusion, into robust spike bursts resembling PDSs (Contreras et al. 1997). In the penicillin model of SW seizures, the hyperpolarizing component (associated with the EEG wave of SW complexes) is diminished or reversed by Cl\(^{-}\), but this action is only exerted on the first 40–80 ms, leaving intact the late part of the hyperpolarization (Fisher and Prince 1977; Giaretta et al. 1987). Thus, although the early, relatively short-lasting part of the SW hyperpolarization seems to be a Cl\(^{-}\)-dependent IPSP, the late, longer-lasting component of the hyperpolarization could be a K\(^{+}\) outward current because of the Ca\(^{2+}\) entry during the strong excitation associated with the spike component of SW complexes. Action potentials are more effectively abolished during the late, than during the early, part of the depth-positive EEG wave component of SW complexes (see Fig. 6A in Steriade 1974). It is fair to state that the ionic nature and precise mechanism(s) of this late part of SW-related hyperpolarization remain(s) unknown, but disinhibition can be one of the underlying factors.

4) The seizure epoch characterized by fast runs, superimposed on a tonic depolarization of the cell, resembles the stereotyped fast rhythm (~10–20 Hz) reported in human temporal lobe epilepsy that may spread to perihippocampal structures and cingulate cortex (Walsh and Delgado-Escueta 1984) as well as in experimental studies of hippocampus, entorhinal cortex, and related structures (Buzsáki 1989; Buzsáki et al. 1991; DeCurtis et al. 1991; Liberson and Akert 1955; Paré et al. 1992). The fact that the fast runs associated with the seizures described here also appear, with the same features, in isolated neocortical slabs (Timofeev et al. 1997, 1998), precludes the possibility that they are imposed on neocortical circuits from the entorhinal cortex. It can be concluded that such fast runs may be generated in a variety of neo-, allo-, and archicortical structures, and imposed from neocortex on thalamic reticular and thalamocortical neurons (see the thalamic reflection of such fast rhythms in Fig. 2 of Steriade and Contreras 1995; Fig. 4 in Steriade and Contreras 1998; and Timofeev et al. 1998). We postulate that the epochs with fast runs arise as a consequence of the increasing depolarization during spontaneously occurring seizures that usually start with isolated or grouped PDSs and are followed by rhythmic SW complexes implicating a progressive entrainment of cortical neurons. That the period with fast runs is indeed associated with the highest synaptic drive is demonstrated by the largest increase in membrane conductance, tested by short hyperpolarizing current pulses, during the depolarizing plateau of SW seizures (unpublished observations). The transition from rhythmic SW complexes to fast runs may also be attributed to relations between neurons and glial cells. The depolarizing shifts in the latter greatly outlast the decay phase of PDS in the former, and the repolarization in glial cells may take up to 5 s or they even do not repolarize back to the baseline before the onset of the next neuronal PDS (Ayala et al. 1973; see also Amzica et al. 1997).
so, the accumulation of K\textsuperscript+ in the extracellular space may favor the transformation of SW seizures into epochs with prolonged depolarizing plateaus. Because the frequency of fast runs is similar or identical to that of polyspikes in PSW complexes (see Fig. 7D and 12), a parsimonious explanation of these related phenomena would be that, at the depolarized levels at which polyspikes develops into uninterrupted fast runs, the conductance underlying the hyperpolarization that forms the SW complex is inactivated. Finally, the epoch of steady depolarization with fast runs may also be assisted by intrinsic properties of neocortical neurons, such a persistent, noninactivating Na\textsuperscript+ current sculpted by a delayed rectifier, similarly to the ionic nature of intrinsic oscillations faster than 10 Hz in guinea pig frontal neurons (Llinás et al. 1991).

Concluding remarks

Data presented in the present study support the notion that at least some types of seizures, that consist of SW/PSW complexes (2–3 Hz) and faster components (10–15 Hz), preferentially emerge without discontinuity from sleep patterns and that similar relations between EEG and intracellular activities exist during the slow sleep oscillation and the subsequent paroxysmal events. It should be emphasized that by sleep patterns we mean the cortically generated slow oscillation at <1 Hz (that has the same basic features and frequencies in cats and humans) but not the thalamically generated sleep spindles, because the preceding paper has demonstrated that similar seizures occur intracortically after thalamectomy. Because of their propensity to high-frequency rhythmic spike bursts, FRB cells may play a crucial role in the synchronization and possibly in the initiation of these seizures. The EEG patterns of seizures investigated intracellularly in the present study resemble those that are associated with the Lennox-Gastaut syndrome. In the next papers, we will present data related to the intracortical synchronization of these seizures and to the mechanisms of fast components reflected in thalamic neurons.

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REFERENCES

Achermann, P. and Borbély, A. A. Low-frequency (<1 Hz) oscillations in the human sleep EEG. *Neuroscience* 81: 213–222, 1997.


