Spike-Wave Complexes and Fast Components of Cortically Generated Seizures. I. Role of Neocortex and Thalamus

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Steriade, Mircea and Diego Contreras. Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus. J. Neurophysiol. 80: 1439–1455, 1998. We explored the relative contributions of cortical and thalamic neuronal networks in the generation of electrical seizures that include spike-wave (SW) and polyspike-wave (PSW) complexes. Seizures were induced by systemic and local cortical injections of bicuculline, a γ-aminobutyric acid-A (GABA_A) antagonist, in cats under barbiturate anesthesia. Field potentials and extracellular neuronal discharges were recorded through arrays of eight tungsten electrodes (0.4 or 1 mm apart) placed over the cortical suprasylvian gyrus and within the thalamus. 1) Systemic injections of bicuculline induced SW/PSW seizures in cortex, whereas spindle sequences continued to be present in the thalamus. 2) Cortical suprasylvian injection of bicuculline induced focal paroxysmal single spikes that developed into full-blown seizures throughout the suprasylvian cortex. The seizures were characterized by highly synchronized SW or PSW complexes at 2–4 Hz, interspersed with runs of fast (10–15 Hz) activity. The intracellular aspects of this complex pattern in different types of neocortical neurons are described in the following paper. Complete decortication abolished the seizure, leaving intact thalamic spindles. Injections of bicuculline in the cortex of athalamic cats resulted in similar components as those occurring with an intact thalamus. 3) Injection of bicuculline in the thalamus decreased the frequency of barbiturate spindles and increased the synchrony of spike bursts fired by thalamocortical and thalamic reticular cells but did not induce seizures. Decortication did not modify the effects of bicuculline injection in the thalamus. Our results indicate that the minimal substrate that is necessary for the production of seizures consisting of SW/PSW complexes and runs of fast activity is the neocortex.

INTRODUCTION

The present and companion studies demonstrate the neocortical origin of electrical seizures consisting of spike-wave (SW) or polyspike-wave (PSW) complexes at 2–4 Hz, often associated with fast runs at 10–15 Hz. These electrical patterns strikingly resemble those reported in some forms of epileptic seizures with SW/PSW complexes, accompanied or not by fast runs. Still, a distinction should be made between an electrical pattern and a disease entity. Although SW seizures are often regarded as homologous with absence (petit-mal) epilepsy, absence epilepsy should remain a clinical notion. Nonetheless, in view of the highly stereotyped patterns of SW/PSW complexes and fast runs, we postulate that the cellular patterns described here may also underlie similar electroencephalogram (EEG) aspects occurring in different forms of epileptic seizures. In this series of four papers, we performed an investigation of cortically initiated seizures consisting of SW/PSW complexes and fast runs by using extra- and intracellular recordings of single neurons as well as dual intracellular recordings from neocortex and thalamus in acutely prepared animals, and extracellular recordings in behaving animals.

The relative roles played by thalamic and cortical neuronal networks in the generation of seizures with SW or PSW EEG complexes recurring rhythmically at 2–4 Hz, as in absence (petit-mal) epilepsy, have been debated. In earlier experiments, 3-Hz stimulation of the medial thalamus induced SW-like responses in the cortex, without leading to self-sustained activity (Jasper and Droogleever-Fortuyn 1947) or inducing a single outlasting SW complex (Pollen et al. 1963). On the basis of those data, it was assumed that the thalamus generates this form of seizures. Subsequently, repetitive thalamic stimulation led to self-sustained cortical SW seizures during drowsiness or light sleep of behaving primates, lasting for periods of 10–15 s and accompanied by tonic eyelid movements (Steriade 1974), similarly to patterns observed in clinical absence seizures. Such seizures also occurred spontaneously. Because of the focal cortical manifestation of those paroxysms, we have postulated that the neocortex plays a leading role in the generation of at least some types of SW seizures. Subsequent studies, using the feline generalized penicillin epilepsy model, have also proposed that SW seizures are initiated in cortex (Fisher and Prince 1977) and represent transformation of thalamocortical spindles at an increased level of cortical excitability (Gloor et al. 1990). The active role of intracortical circuitry in the EEG expression of thalamically generated spindles and related SW patterns was also emphasized by Kandel and Buzsáki (1997).

The idea of a prevalent participation of the cerebral cortex in the generation of spontaneously occurring SW seizures, developing from sleep patterns, was strengthened by using simultaneous intracellular recordings from cortical and thalamic neurons in vivo. Thus it was demonstrated that a majority of thalamocortical (TC) cells are steadily hyperpolarized during cortical SW-type paroxysms, due to the rhythmic spike bursts of GABAergic thalamic reticular (RE) neurons driven by corticothalamic volleys (Steriade and Contreras 1995; see also the modeling study of those experimental data by Lytton et al. 1997). We have suggested that the inhibition of TC cells and their incapacity of relaying incoming signals in their route to cortex may explain the impairment of consciousness during SW seizures.

The classical definition of clinical absence seizures implies suddenly generalized, bilaterally synchronous SW complexes at ~3 Hz. Although they may appear to be simultaneous at a visual inspection of EEG traces, cellular re-
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FIG. 2. Initial signs of paroxysmal activity after bicuculline injection in cortex of a brain-intact animal. Brain figure shows location of 8 macroelectrodes in the suprasylvian gyrus and the site of bicuculline injection (between electrodes 4 and 5). One minute after injection, single and multiple EEG spikes appeared in closely located foci (Cx 4 and Cx 5), while the other leads continued to display spindle sequences.

cordings rather indicate that the buildup of electrical SW seizures obeys the rule of synaptic propagation through short- and long-scale circuits (Steriade and Amzica 1994). These cellular findings corroborate earlier clinical data showing differences in time occurrence between EEG SW complexes recorded from various cortical foci (Jasper and Hawke 1938) and multiple, independent generators of SW complexes resulting from toposcopic analyses in patients with absence seizures (Petsche 1962). The variety of seizures displaying SW patterns cannot be overemphasized. In some clinical cases, SW complexes occur at lower (1–2 Hz) or higher (4–6 Hz) rates than the classical frequency (~3 Hz). Most electrical seizures described in the present series of studies resemble the EEG pattern reported in the Lennox-Gastaut syndrome, with episodes of SW and PSW complexes associated with fast runs of EEG spikes (Dreifuss 1990; see also Fig. 14.7 in Niedermeyer 1993). We also analyzed cortical seizures consisting of pure SW complexes at 3–4 Hz (see Figs. 1 and 2 in the next paper).

The present series of four studies is organized in the follow-

FIG. 1. Intact-cortex hemisphere has a lower threshold for seizure initiation, induced by systemic injection of bicuculline, than the decorticated one. A and B: 4 multiunit thalamic recordings from left decorticated hemisphere (Left Th 1 to 4; interelectrode distance was 0.4 mm) showing spike bursts corresponding to spindle sequences. Two bottom traces are bipolar electroencephalogram (EEG) traces from precuneate (Right Cx prec.) and posterior suprasylvian (Right Cx post. ssylv.) in the right (intact) hemisphere showing spontaneous spindle oscillations. After the injection of intravenous bicuculline (arrow, Bic. i.v.), paroxysmal spikes preferentially appear on the EEG during spindle oscillations (asterisks) until a full-blown cortical seizure dominates the EEG, displaying spike-wave (SW) complexes at ~3 Hz (arrow in B indicates expanded trace with SW complexes). Thalamic leads showed virtually no alteration of normal spontaneous spindling activity.
ing order. In the first paper we tested the hypothesis that SW
seizures emerge from thalamically generated sleep spindles.
We conducted experiments under barbiturate anesthesia to
produce reliable spindle sequences, and we used a model of
acute epileptogenesis based on injections of the \( \gamma \)-aminobutyric acid-A (GABA\(_A\)) blocker biccuculline, either systemic or localized within the neocortex or thalamus. We made simul-
taneous extracellular recordings of neurons and field po-
tentials from the cortex and thalamus, and we performed com-
plete unilateral ablations of the cortex or thalamus. Data show
that there are mechanisms within the cortex that generate
the major components of seizures consisting of SW or PSW
complexes (2–4 Hz) and fast runs (10–15 Hz) of EEG
spikes. Such seizures survive thalamectomy and, thus, are not
dependent on spindle oscillations. Injections of biccuculline
within thalamus enhance spindle synchrony and related spike
bursts but do not produce SW seizures. Having demonstrated
the crucial role of the neocortex in the generation of seizures
with SW/PSW complexes and fast runs, in the second study
we conducted experiments on chronically implanted cats to
validate the patterns of seizures in behaving animals, and
we performed intracellular recordings to reveal the neuronal
substrates of the two major components of seizures (SW/
PSW complexes and fast runs). In the second as well as
following papers, single and dual simultaneous intracellular
recordings from cortex or from cortex and thalamus were
performed in conjunction with multisite field potentials and
extracellular unit discharges under ketamine-xylazine anesthe-
sia, because it was recently demonstrated that this anesthesia
reproduces the pattern of natural slow-wave sleep (Steriade et al. 1996), a state during which SW seizures preferentially
occur. The third paper deals with the synchronizing mecha-
nisms of these cortically generated seizures, and the fourth
one investigates the reflection of these seizures in RE and TC
neurons, with emphasis on the cellular mechanisms of fast
runs.

METHODS

Preparation

Experiments were conducted on 42 adult cats (2.5–3.5 kg),
anesthetized with pentobarbital sodium (35 mg/kg ip). The tissues
to be incised and pressure points were infiltrated with lidocaine.
The animals were paralyzed with gallamine triethiodide and artifi-
cially ventilated while monitoring the end-tidal CO\(_2\) concentra-
tion at 3.5–3.8%. A permanent sleeplike state, as ascertained by contin-
uous recording of the EEG, was maintained by administering addi-
tional doses of the same anesthetic during the experiments. Heart
rate was continuously monitored, and body temperature was main-
tained at 37–39°C. The stability of recordings was ensured by cisternal drainage, hip suspension, and by filling the hole made in
the calvarium with a solution of agar (4%).

Left hemidecortication was performed by suction after complete
exposure of the hemisphere. Removal of the left thalamus was
done either acutely by suction (entering through the right hemi-
sphere and midline) or by kainic injections 2 days before the
experiment (for histological aspects of thalamic excitotoxic lesions
and decortication, see Fig. 10 in Steriade et al. 1993b; and Fig. 1
in Steriade and Timofeev 1997).

Recording and stimulation

Gross cortical EEG was recorded monopolarly by means of
screws inserted into the bone over the pericruciate and suprasylvian
areas of the right hemisphere. focal thalamic epileptiform activ-
ity was exposed and bathed in mineral oil to prevent desiccation.
Left thalamic recordings were performed by lowering the electrode
array through the marginal gyrus, or directly penetrating the thal-
amus after total decortication of the ipsilateral hemisphere.

Recording of focal EEG, electrothalamogram (ETHG), and thal-
amic neuronal activity was performed with two types of electrodes:
1) arrays of eight tungsten microelectrodes (tip resistances ~3–8
M\(_{\Omega}\)) held together in parallel, with constant interelectrode
tances of either 0.4 or 1 mm; and 2) concentric bipolar electrodes
of low resistance, with desizedtulated tip and ring of 0.1 mm each,
separated by 0.7 mm. The bipolar electrodes were placed to have
the ring over the surface of the suprasylvian gyrus. For monopolar
recordings the indifferent electrode was placed in the neck muscles.

For bipolar (tip-ring) recordings in the cortex, the polarity was
adjusted to match that of the depth-EEG (positivity up). Unit and
multunit activities were recorded from RE, ventral lateral (VL),
lateral posterior (LP), and rostral intralaminar central lateral (CL)
thalamic nuclei. That LP and CL nuclei are reciprocally connected to areas 5–7 in the suprasylvian gyrus has been shown both mor-
phologically (Jones 1985) and electrophysiologically (Steriade and
Glenn 1982; Steriade et al. 1993a). Signals were recorded on an
eight-channel tape with band-pass of 0–9 kHz and digitized at 250
Hz or 10 kHz for off-line computer analysis of waves and spikes,
respectively. Subsequent filtering of data was performed digitally.

Stimulation of the cortex and thalamus was performed through
the same bipolar electrodes as used for recordings. For cortical
stimulation, two bipolar electrodes were placed by visual inspection
in the most anterior and posterior aspects of the suprasylvian gyrus
at a distance of 15 mm from each other. For thalamic stimulation,
a bipolar electrode was placed stereotaxically in the LP nucleus
(A8 to A9, L5 to L6, D3 to D4).

At the end of the experiments, the cats were given a lethal
dose of pentobarbital. The locations of recording and stimulation
electrodes, and the extent of decortication and thalamectomy, were
verified on frontal 80-\(\mu\)m sections stained with thionine.

RESULTS

Systemic injections of biccuculline

The first approach in determining the relative contribu-
tions of cortical and thalamic networks in the generation of
seizures after blockade of inhibition consisted of injecting systemically the GABA<sub>A</sub> antagonist bicuculline (2 mg/kg) in animals in which the cortex of the left hemisphere was completely removed while the cortex of the right hemisphere was left intact (n = 9). Recordings were made from the left thalamus of the decorticated hemisphere by means of four microwires separated by 0.4 mm in the anteroposterior axis, covering the VL and LP nuclei. Simultaneously, cortical activity was recorded from the right precuneate and posterior suprasylvian cortices by means of bipolar electrodes with the ring at the surface and the tip in the depth (Fig. 1). Before the intravenous injection of bicuculline, thalamic multiunit recordings revealed spike bursts corresponding to spontaneous spindle sequences that were also present in the depth-EEG from the contralateral precuneate and suprasylvian cortices. Despite the absence of cortex at the left, a condition that diminishes the spatiotemporal coherence of thalamic spindles and tends to disorganize them (Contreras et al. 1997), thalamic spindle sequences occurred in close time relation because of the proximity of recording sites (Contreras et al. 1996; Timofeev and Steriade 1996). Systemic injection of bicuculline (Fig. 1A, Bic. i.v.) led to the appearance of high-amplitude, isolated spikes in the right suprasylvian cortical EEG (Fig. 1A, asterisks). Subsequently, within 1–3 min, a full-blown seizure appeared in both right cortical foci (Fig. 1B). The seizure lasted for 70 s and consisted of fast EEG spikes at ~10–12 Hz and SW complexes at ~3 Hz (Fig. 1B; SW complexes are expanded below). In contrast, thalamic activity in the decorticated hemisphere was unaffected, although some additional spike activity could occasionally be observed on the background of ongoing spindling (see B, left).

To sum up, systemic injections of bicuculline induced seizures in intact corticothalamic networks, whereas rhythmic sequences of spindle oscillations continued to be present in the thalamus of the decorticated hemisphere.

Local injections of bicuculline in cortex

Given the lower threshold for SW seizure of the intact hemisphere, as compared with the decorticated one (Fig. 1), we attempted to reproduce the same sequence of events leading to seizures by injecting small amounts of bicuculline (0.1 μl, 0.2 mM) in the depth of the suprasylvian cortex (n = 14). Such focal injections induced cortical paroxysms with similar characteristics to those induced by systemic injections, namely, isolated EEG spikes (Fig. 2) followed after a few minutes by full-blown seizures consisting of fast EEG spikes (10–15 Hz) and SW complexes at 2–4 Hz (see below).

To determine the participation of the thalamus during the seizures induced by bicuculline injections in the suprasylvian cortex, we recorded simultaneously from several thalamic and cortical sites in 9 of those 14 experiments. Multiunit activity was recorded from the left thalamus through anteroposterior arrays of four to eight tungsten electrodes, with interelectrode distances of 1 mm, and showed sequences of spike bursts within the frequency range of spindle oscillations (Fig. 3, see Left Th1 to 3, before bicuculline injection). Cortical activity was recorded through EEG electrodes placed in the depths of anterior and posterior parts of the left suprasylvian gyrus (areas 5 and 7, respectively) and in the right precuneate gyrus, contralateral to thalamic recordings. The spontaneous spindle oscillations from cortical areas 5–7 were in close time relation with those from the multiunit thalamic recordings (see Fig. 3, top left). After the injection of bicuculline in the posterior third of the suprasylvian gyrus (see brain figure in Fig. 3), EEG spikes appeared initially in the posterior suprasylvian gyrus (asterisks in top right). The bicuculline-induced cortical EEG spikes were accompanied by high-frequency spike bursts followed by long periods of silence in the thalamus, initially in electrodes Th2 and Th3 located in the LP nucleus. After a few minutes, EEG spikes were present in both left cortical leads and were reflected in thalamic electrodes as spike bursts followed by neuronal silence (Fig. 3, bottom left). The number of isolated EEG spikes increased progressively until SW complexes of 2–4 Hz appeared in the EEG. The cortical SW complexes were reflected as spike bursts or single spikes in 40–45% of the recorded thalamic neurons (Fig. 3, see detail indicated by arrow in the bottom right panel). The remaining TC cells were silent throughout cortical SW seizures, as previously described (Steriade and Contreras 1995). Interestingly, out of five thalamic leads, only Th2 and Th3 maintained close time relations with isolated cortical EEG spikes and with the spike component of cortical SW complexes, probably because of the anatomic connectivity between areas 5–7 and LP nucleus (Jones 1985). Such phase relations in corticothalamic networks are also seen with sleep oscillations (Contreras and Steriade 1996).

Within 5–10 min after the cortical injection of bicuculline, a stable EEG pattern of seizure activity was reached, with generalized paroxysmal activity in corticothalamic networks (Fig. 4). The basic features of seizures were as follows. After isolated single spikes and/or a few SW complexes, runs of fast activity (mainly 10–15 Hz) with lower amplitudes appeared. Thereafter, the seizure components slowed down to SW complexes at 2–4 Hz with increased wave amplitude. This pattern of recurrent seizures was reflected in thalamic territories (VL, CL, and LP nuclei, Th1 to Th3 in Fig. 4) by spike bursts that were coincident with the depth-negative peaks of cortical EEG spikes (Fig. 4). Although in some cases the fast runs (10–15 Hz) preceded the SW complexes at 2–4 Hz, the opposite was also observed, and, during protracted seizures, the two basic components (fast runs and SW complexes) were alternating.

Corticothalamic dissociation

Although some thalamic foci displayed seizure activities that were closely related to cortical ones (see above, Fig.
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4), careful exploration of the thalamus revealed territories that did not participate in seizures but still generated spindling activity while the cortex was engaged in seizure patterns (Fig. 5). Such thalamic territories varied in size, spanning from three to six electrodes (2–5 mm), and were prevalently located in the ventral parts of VL and LP nuclei. In those thalamic foci that preserved normal spindle oscillations, the sequences of spindles were triggered by low-frequency, isolated cortical EEG spikes (interictal spikes) that initiated the seizures. In seven experiments, spindles were transiently blocked at the end of the fast EEG runs (Fig. 5A). The analysis of temporal relations between cortical EEG paroxysmal spikes and multiunit activities related to spindling in the thalamus showed that cortical EEG ictal spikes preceded the onset of spindle-related thalamic discharges by 0.2–0.5 s (Fig. 5B). Importantly, the ablation of the epileptic cortex left a thalamus that exclusively displayed spindling, with no signs of seizure activity, thus indicating that even hours of continuous seizure activity left no secondary focus in the thalamus (n = 6).

Local injections of bicuculline in the thalamus

The above data show that the cortex plays an essential role in the generation of epileptic seizures after blockade of inhibition, because 1) small injections of bicuculline in the cortex gave rise to full-blown seizures containing SW complexes (2–4 Hz) and runs of fast EEG spikes (10–15 Hz) while the thalamus remained in the spindling state (see Fig. 5A) and 2) the thalamus of the decorticated hemisphere did not show epileptic activity after systemic injection of bicuculline (see Fig. 1).

We then proceeded to inject bicuculline in restricted thalamic territories to determine the possible co-participation of the thalamus in this type of seizures (n = 16). As shown in the Fig. 6, top, depicting three thalamic sites (Th1 to Th3, 2 in VL and the 3rd in CL), the spindle-related spike bursts occurred in close relation with EEG spindles from precruciate cortex (Cx precr.). About 20 min after an injection of bicuculline between Th2 and Th3, the following changes were observed (see bottom panel in Fig. 6): 1) the number of action potentials per spike burst increased in all cells; 2) the repetition rate of spike bursts decreased from that of spindling (∼10 Hz) to ∼4 Hz; 3) the synchrony of spike bursts between cells increased; and 4) a cortical EEG also showed a slowed frequency and increased amplitude of spindles, but no paroxysmal pattern (Fig. 6) compared with the bona fide SW seizures depicted in Figs. 1 and 3–5. This result is similar to the slowed spindles reported in thalamic slices from ferrets (Bal et al. 1995). In conclusion, thalamic injection of bicuculline induced a pattern of highly synchronous slowed spindling, but not SW seizures (see criteria for defining seizures in DISCUSSION).

To study the role of the RE nucleus in the synchronization of thalamic units during the slowed (4 Hz) spindle oscillation after focal bicuculline injections in the thalamus, we made such injections in the rostrolateral sector of the RE nucleus (n = 4). Figure 7 summarizes such an experiment in which multiunit activity is represented by rate meters (number of spikes from 0.1-s bins). The first recording microelectrode was glued to the syringe to electrophysiologically guide the injection by monitoring the typical neuronal activity in the RE nucleus (prolonged spike bursts with accelerando-decelerando patterns) (see Domich et al. 1986; Steriade et al. 1986). The other three electrodes were placed more posteriorly (within VL, CL, and LP thalamic nuclei), at 1-mm intervals. At a condensed time scale, the effect of bicuculline was visible by increased firing rates preceded by a transient decrease in discharge frequency (see TC 1 in top left panel of Fig. 7). This effect was exerted progressively from the RE nucleus toward more posterior sites, suggesting that the effect of bicuculline spread at a velocity of ∼0.1 mm/min. In the details shown in Fig. 7 (A–E), the progressive effect of bicuculline is visible by the increase in firing rate, decrease of the repetition rate of spindle oscillation, and, more importantly, by a dramatic decrease in the variability of the initiation time of oscillations among the different electrodes.

The rhythmicity and cellular relations shown in Fig. 7, before and after bicuculline injection, were evaluated by means of auto- and cross-correlograms (Fig. 8). Before the injection, the fluctuations from spindle to spindle sequences and the multiunit nature of the recordings blurred the autocorrelograms (AUTO), although rhythmic activity around 7 Hz was visible in the RE neuronal population. Bicuculline (Bic., arrow) induced a strong rhythmic (4 Hz) pattern in all cells. The appearance of 4 Hz rhythmicity in the RE nucleus (at 20°) followed the changes in the first dorsal thalamic electrode (TC1, at 10°), although the increase in firing rate first occurred in the RE nucleus. Rhythmic activity induced by bicuculline was strongly correlated among all cells (Fig. 8, CROSS).

Athalamic cats

To ascertain whether the cortex alone is capable of generating the epileptic patterns observed in intact animals, we performed recordings from the cortex of animals where the thalamus was removed by suction or by excitotoxic lesions using injections of kainic acid 2 days before recordings (see Fig. 10 in Steriade et al. 1993b). After unilateral thalamectomy (n = 3), the cortical EEG from the ipsilateral (left) suprasylvian cortex had little spontaneous activity and showed no spindling. Injection of bicuculline in the left su-
FIG. 6. Local injection of bicuculline in the thalamus decreases the frequency of ongoing spindle oscillations. Top panel: 3 thalamic multiunit recordings (Th1 to Th3) from foci separated by 2 mm revealed spike bursts corresponding to spontaneous spindle oscillations that are reflected in the EEG from the ipsilateral precruciate cortex (Cx precr.). Bottom panel: injection of bicuculline between thalamic electrodes 2 and 3 increased the number of action potentials per burst and reduced the frequency of spindling from 10 to 4 Hz; this reduction in spindle frequency was also reflected in the cortical EEG.
prasyvian cortex induced seizures with patterns that were similar to those observed in intact-brain animals, i.e., containing fast runs at 10–15 Hz that slowed down to SW or PSW complexes at 2–4 Hz (Fig. 9). Athalamic animals showed the distinctive characteristic of displaying long sequences (1–2 min up to 6–7 min) of continuous SW activity at 2–4 Hz, with a spectacular synchronization across all cortical leads (Fig. 10).

**Fig. 7.** Spread of bicuculline in the thalamus is reflected by the decreased frequency and increased synchrony of spindle oscillations. Four microelectrodes were inserted in the thalamus of an ipsilaterally decorticated cat, with interelectrode distances of 1 mm. The most anterior electrode was in the rostral pole of the reticular (RE) nucleus, and the 3 next electrodes were in the VL, CL, and lateral posterior nuclei. Rate meters from the multunit recordings (bin = 0.1 s; calibration in A represents number of spikes per bin). Injection of bicuculline (Bic.) was close to the RE nucleus and then spread through the thalamus inducing a transient decrease in discharge rate (~250 ms after Bic. injection; see top left panel), followed by a sustained increase in firing rate. Points indicated by A–E are expanded in the other panels, showing the increase in the number of spikes per burst and the intrathalamic synchrony.
FIG. 8. Auto- (AUTO) and cross-correlograms (CROSS) of cells shown in Fig. 7. Spikes for analyses are from periods of 2 min (bin = 100 ms) taken from before (left column) and 10, 20, and 35 min after the injection of bicuculline (Bic., arrow; columns to the right). Diffusion of bicuculline in the thalamus slowed the frequency of spindles to 4 Hz and dramatically increased cellular synchronization.
FIG. 9. Patterns of cortical EEG seizures, similar to those in intact-brain animals, are generated in cortex after ipsilateral (left) thalamectomy. A: isolated paroxysmal spikes appeared in the suprasylvian gyrus of thalamectomized animal after a local injection of bicuculline between electrodes 4 and 5. The EEG from the contralateral (right) precruciate gyrus showed spontaneous spindling (see detail at right). B: increase in spikes' frequency led to EEG seizures consisting of fast runs of spikes (10–20 Hz) and polyspike-wave complexes (~2 Hz). This pattern is similar to that illustrated in Fig. 4 from an animal with intact thalamus.

DISCUSSION

Data show that 1) bicuculline-induced seizures, consisting of SW or PSW complexes at 2–4 Hz and episodes with fast components (10–15 Hz), are initiated in the cerebral cortex, whereas the thalamus can simultaneously display normal spindle oscillations; 2) similar seizures can be induced in the cortex of thalamic animals; and 3) bicuculline injections into the thalamus of decorticated cats alter spindles by producing more action potentials and lower frequency of spike bursts, but not seizures (see below definition of seizures).

Experimental model

Although SW or PSW complexes at 2–4 Hz constitute the electrographic correlate of some epileptic seizures in humans and behaving animals, we simply use the term electrical seizure and do not consider it as necessarily homologous to different forms of clinical epilepsy because the present experiments were conducted under barbiturate anesthesia and seizures were induced by bicuculline. The heterogeneity of clinical aspects and EEG correlates of the so-called “typical absence seizures” (Panayiotopoulos et al. 1989) is such that their classification may serve descriptive purposes, but defies attempts to establish definite categories. Although absence epilepsy should remain a clinical notion, the typical electrographic patterns are rhythmic (2–4 Hz) SW or PSW complexes, whose origin has been investigated here under barbiturate anesthesia and whose intracellular counterparts are reported in the following studies of this series conducted under other anesthetics (ketamine and xylazine). Very simi-
Prolonged SW patterns appear in cortex after ipsilateral thalamectomy. Seizure patterns induced by local injection of bicuculline in the left suprasylvian cortex after unilateral (left) thalamectomy. Note the appearance of extremely long runs (~5 min duration) of cortical SW complexes at 2–4 Hz. The EEG from the contralateral precuneate cortex and VL nucleus showed spontaneous spindling.

**Fig. 10.** Prolonged SW patterns appear in cortex after ipsilateral thalamectomy. Seizure patterns induced by local injection of bicuculline in the left suprasylvian cortex after unilateral (left) thalamectomy. Note the appearance of extremely long runs (~5 min duration) of cortical SW complexes at 2–4 Hz. The EEG from the contralateral precuneate cortex and VL nucleus showed spontaneous spindling.

Other aspects also occur in chronically implanted animals, during different stages of the natural wake-sleep cycle (Steriade 1974) (see also Figs. 1–3 in the next paper). Below, we address two points, one related to the term *seizure*, the other related to the action(s) of bicuculline in blocking GABA<sub>A</sub> receptors and some intrinsic currents in thalamic and cortical neurons.

1) We mean by seizure a transient episode whose electrical signs, consisting of highly increased amplitudes and altered frequencies of EEG waves, are in sharp contrast with the background activity. Even when seizures emerge without discontinuity from sleep patterns, they have a sudden end and are followed by postictal depression in intracellular (but not necessarily EEG) recordings (see the next paper by Steriade et al. 1998). These features stand in contrast with other forms of oscillatory activity that are characterized by altered frequencies and/or amplitudes of electrical events, without, however, being paroxysmal. This is the case of slowed spindles induced by bicuculline injections in the thalamus (see Fig. 6) (also Bal et al. 1995), which are not seizures but continuously and regularly recurring, cyclic oscillations whose only differences from spindles are the slowed frequency and increased number of action potentials in spike bursts. As defined by McNamara (1994), a seizure may be “epileptic” when occurring without apparent provocation (as is the case in the following paper, dealing with spontaneously occurring paroxysms that have a pattern similar to the present ones induced by bicuculline) or “nonepileptic” when evoked by chemical convulsants. The cortical SW seizures illustrated here are similar in duration, patterns, and frequencies of SW complexes to those associated with tonic eyelid blinking during drowsiness in behaving monkeys (Steriade 1974). At variance with the “suddenly generalized, bilaterally synchronous” character of seizures that is conventionally thought to define SW complexes associated with absence attacks in humans, the seizures described here and in the following papers are partial, initiated in cortex, and often sparing the thalamus (see below).

2) Bicuculline, a GABA<sub>A</sub> receptor antagonist, readily induces seizure patterns through disinhibitory actions leading to
exceedingly enhanced excitatory inputs. This substance has also been used to induce seizure-like activity in cortical slices (Chagnac-Anmitai and Connors 1989; Gutnick et al. 1982). Recent work on thalamic and hippocampal neurons showed that bicuculline-M (methiodide, methobromide, and methochloride, as employed in the present experiments), thought to specifically antagonize GABA_A receptors, also directly blocks the low-threshold spike-burst afterhyperpolarization (Debarbieux et al. 1998). This effect on small conductance channels would lead to the prolongation of spike bursts and may additionally contribute to an increased propensity for seizures.

Seizures are initiated in the cerebral cortex and survive thalamectomy

One of the major findings in our study was the initiation of seizures within the cerebral cortex and their persistence in athalamic animals. That spontaneously occurring SW seizures are initiated (and sometimes localized) within the cortex has previously been observed with extracellular recordings in behaving monkeys (Steriade 1974) and with intracellular recordings in cats maintained under anesthesia (Steriade and Amzica 1994; Steriade and Contreras 1995). In the latter studies, multisite recordings showed that the thalamus lagged behind the cortex by a few seconds. Similar findings have been reported in the acute model of penicillin-induced generalized SW seizures (Prince and Farrell 1963) during which cortical hyperexcitability may favor the development from spindles into SW seizures (Gloor et al. 1990). In those cases, the SW rhythm appears in the cortex before the thalamus (Fisher and Prince 1977), and the reverse has never been seen (Gloor and Fariello 1988). All these data congruently show the leading role of cortex in the development of SW seizures.

The present results indicate not only normal spindling activity in the thalamus during bicuculline-induced cortical seizures (Figs. 1 and 5) but also the presence of SW seizures in the cortex of athalamic animals (Figs. 9 and 10). These data demonstrate that the neocortex is the minimal substrate necessary for the production of SW paroxysmal activity. In humans too, SW complexes (average rate of 3.5 Hz), occurring during wake and sleep states or with hyperventilation, arise in cortex and are usually propagated within the same hemisphere from lateral and posterior to more anterior sites as well as to the opposite hemisphere through the corpus callosum (Lemieux and Blume 1986). The short interhemispheric propagation time in that study (average as short as 6 ms and some delays up to 25 ms) led to the conclusion that the thalamus does not play a pivotal role in the propagation of SW seizures.

Thus the intrahemispheric and callosal projections contribute to the generalization of SW seizures. In fact, no thalamic or other deeply lying system is known to possess the required bilateral projections to cortex that would be necessary for the appearance of a “suddenly generalized, bilaterally synchronous” seizure. As to the bilateral projections of brain stem activating systems, which implicate both hemispheres, they lead to supression, not generation, of SW seizures (Danobe et al. 1995).

Thalamic events during cortically generated seizures

Despite accumulating evidence in favor of the idea that SW seizures are initiated in neocortex, the electrophysiological properties of RE and TC cells have often been invoked to consider these neuronal types and their synaptic interactions as necessary for the production of SW seizures. It was proposed that a massive thalamic synchronization occurs during an absence seizure (Buzsáki 1991) and, indeed, the regional blood flow increases in the thalamus during typical SW seizures in humans (Prevett et al. 1995). These data corroborate additional data from animals, showing that 40% of TC cells actively participate in SW seizures; however, the majority of TC cells are continuously hyperpolarized and silent during these paroxysms (Steriade and Contreras 1995; see also Pinaud et al. 1998).

Various models of SW seizures in rodents have reported the preferential involvement of midline (Hosford et al. 1995) or GABAergic RE (Avanzini et al. 1993) neurons in the generation of SW seizures. In the Strasbourg rat model of generalized absence epilepsy (Marescaux et al. 1992), circumscribed inactivation of the RE nucleus abolished SW discharges (Avanzini et al. 1993). Also, the transient Ca^{2+}-current (I_T), which is a key factor for the generation of rhythmic patterns in thalamic neurons (see Steriade et al. 1997) and has peculiar features in RE neurons (Destexhe et al. 1996; Huguenard and Prince 1992), is selectively increased in GABAergic RE neurons from rats that display the genetic absence epilepsy (Meis et al. 1996; Tsakiridou et al. 1995). However, even when rhythmogenesis is generated in local thalamic networks, cortical inputs are crucial in synchronizing the seizure activity on a larger spatiotemporal scale (Seidenbecher et al. 1998), as is also the case for sleep spindles (Contreras et al. 1996, 1997). And RE neurons, which faithfully follow every paroxysmal event during cortical seizures, produce steady hyperpolarizations and phasic inhibitory postsynaptic potentials (IPSPs) in TC cells, rather than rebound spike bursts, because of rapid and coalescing IPSPs that prevent the generation of low-threshold spike bursts because of increased conductance (Lytton et al. 1997; Steriade and Contreras 1995).

As to the action of ethosuximide, a drug that is specifically active in the treatment of absence epilepsy, it was demonstrated that it partially blocks the Ca^{2+}-dependent T-current in TC cells (Coulter et al. 1989, 1990; Huguenard and Prince 1994). In view of the present data supporting the cortical initiation of SW seizures, and the presence of Ca^{2+}-mediated low-threshold responses in cortical pyramidal and nonpyramidal neurons (Kawaguchi 1993; de la Peña and Geijo-Barrientos 1996), the possibility that ethosuximide also acts at the cortical level should be explored.

Concluding remarks

The seizures investigated in this study had complex patterns consisting of SW rhythmic complexes (2–4 Hz) and fast runs (10–15 Hz). They occurred focally in some cortical areas but could spread in some instances to other cortical regions and the thalamus. Because the thalamus was not often implicated in seizures but generally continued to display normal spindle sequences, and in view of data showing
that a majority of TC cells are steadily hyperpolarized during SW seizures (Steriade and Contreras 1995), we conclude that the minimal substrate for the generation of such seizures is the neocortex. However, after disconnection of intracortical synaptic linkages, the rostral intralaminar CL nucleus, with widespread cortical projections (Jones 1985), may synchronize various cortical areas (Neckelmann et al. 1998). This result indicates that the thalamus can play an ancillary role in synchronization of SW seizures after the interruption of intracortical pathways. Another possible role of the thalamus is the potentiation of cortically generated seizures through the backfiring phenomenon, namely, that synchronized paroxysmal discharges in cortex produce antidromic action potentials in TC cells that, in turn, may potentiate the further development of seizures (Gutnick and Prince 1972; reviewed in Huguenard and Prince 1997). The orodromic invasion of the thalamus, through corticothalamic volleys, engages synaptic both RE and TC neurons and further develops the cortically generated seizure through the reciprocal circuits between these two thalamic cellular classes. This view is supported by data showing that, in slices preserving corticothalamic connectivity, a major property of corticothalamic projections is the selective amplification of responses to stimuli at 3 Hz (Kao and Coultier 1997), as is the case with the self-sustained SW afterdischarges at 3 Hz following corticothalamic volleys (Steriade et al. 1976). In fact, the amplification of 3-Hz thalamic responses is compromised in "decorticated" thalamocortical slices (Kao and Coultier 1997).

Finally, the association of SW complexes at 2–3 Hz and fast runs at 10–15 Hz is observed in EEG recordings from patients with the Lennox-Gastaut syndrome (see introduction). A brain biopsy from such a case revealed pathological aspects in cortical neurons from layers V and VI, and the authors suggested a causal rather than a consequent relation to the Lennox-Gastaut syndrome (Renier et al. 1988). In the next paper, we will describe the intracellular activity of neocortical neurons during spontaneously occurring, cortically generated seizures with SW or PSW complexes and fast components (Steriade et al. 1998).

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