INTRODUCTION

Compound seizures consisting of spike-wave (SW) or polyspike-wave (PSW) complexes at 2–3 Hz and fast runs at 10–15 Hz are generated in neocortex, even in the absence of thalamus (Steriade and Contreras 1998). The cellular substrates of SW/PSW complexes and fast runs have been presented in the previous paper (Steriade et al. 1998a). In previous studies, we have placed emphasis on the focal cortical aspects of SW seizures in behaving monkeys (Steriade 1974) and have shown that SW seizures are generated by a progressive synaptic buildup, sequentially distributed through short- and long-scale linkages within the cortex (Steriade and Amzica 1994).

Here, we investigate the synchronization mechanisms of spontaneously occurring and bicuculline-induced seizures by performing single or dual simultaneous intracellular recordings from cat’s association suprasylvian cortical areas 5 and 7, in conjunction with extracellular unit discharges and field potentials recorded from neocortical areas and related thalamic nuclei. Several questions were particularly addressed. 1) As this type of seizure develops from sleep-like patterns, how do the time relations between neurons evolve during transitions from epochs with slow oscillation to different parts of seizures? 2) Do the measures of seizure synchrony depend on the distance between various recorded sites? 3) Is the precession in time between different sites where seizures are expressed a stable phenomenon, or does it change throughout a seizure? 4) As the thalamus reflects the cortically generated seizures, does it contribute to seizure synchronization? The results support the idea that SW seizures originate and develop within intracortical circuits well before thalamocortical neurons are entrained into paroxysms, provide evidence for alternating shifts of leading times between different cortical foci, and also demonstrate that, after intracortical disconnection, thalamic nuclei with widespread cortical projections may assist the processes of synchronization between cortical areas.

METHODS

Preparation, recording, stimulation

Experiments were conducted on 52 acutely prepared animals and were performed with the same recording and stimulation procedures as used in the previous paper (Steriade et al. 1998a). Extracellular and intracellular recordings were performed from association areas 5 and 7, visual areas 17 and 18, thalamic rostral intralaminar central lateral (CL) and lateral geniculate–perigeniculate/reticular (PG/RE) nuclei. Stimulation was applied to cortical areas 5 and 7 and to thalamic CL and lateral posterior (LP) nuclei that are reciprocally related to association areas 5 and 7, as shown by anatomic (Jones 1985) and electrophysiological (Steriade and Glenn 1982; Steriade et al. 1993b) studies.

In addition, we performed in five animals a complete coronal transection at the level of the middle suprasylvian gyrus, between areas 5 and 7. The transection extended into the marginal and ectosylvian gyri, up to a depth of 7–9 mm. A celluloid film was inserted into the transection. In addition to spontaneously occurring paroxysmal activities, we administered bicuculline, a GABA_A antagonist. In two animals, 2 mg/kg bicuculline (dissolved in 1 ml saline) was injected intravenously. In 33 animals a syringe filled with 10 µl of a 0.2-mM solution of bicuculline in saline was inserted in cortex.

The distribution of continuous variables were plotted and assessed for shape and normality. Appropriate parametric and non-parametric tests were used, as specified in RESULTS. All comparisons were two-tailed. Different analyses for determining the time lags between simultaneously recorded neurons are explained in the legends of Figs. 5, 10, and 11.
RESULTS

We expose the results in the following order. First, we present evidence for synaptic linkages between suprasylvian areas 5 and 7 (association cortex) and for connections between these neocortical areas and thalamic CL nucleus. These synaptic connections in intracortical and corticothalamic loops may underlie the synchronization processes of cortically generated seizures consisting of SW/PSW complexes and fast components. Next, we present data on intracortical synchronization of spontaneously occurring seizures and on time delays between neurons recorded simultaneously from anterior and posterior suprasylvian areas. Thereafter, we expose data on synchronization of seizures induced by bicuculline infusion within the cortex. Finally, we present data on disruption of seizure synchronization by intracortical transections, and we show that, under this condition, thalamocortical volleys contribute to the partial recovery of seizure synchronization.

Database and identification of intracortical and corticothalamic linkages

A total of 1,530 seizures were recorded. Of those, 149 occurred spontaneously and 267 after electrical stimulation; they also constitute part of the database in the preceding paper (Steriade et al. 1998a). Besides, 1,114 seizures were induced by spontaneous diffusion or deliberate injection of bicuculline. The seizures consisted of SW/PSW complexes at 1.5–3 Hz and runs of activity at 10–15 Hz, as described in the preceding paper. We performed stable intracellular recordings from 221 neurons. In 160 seizures we recorded simultaneously from 2 intracellularly recorded neurons (48 cell couples).

The experimental design used to reveal the intracortical and corticothalamic connectivity that was explored in this paper is illustrated in Fig. 1A. Stimulation in area 7 activated monosynaptically (~1 ms latency) a cell recorded from area 5 and also induced short-latency excitation in the related thalamic nucleus, as seen from the negative field potential recorded from the CL nucleus (Fig. 1B1). Similar synaptic linkages within the suprasylvian gyrus resulted from stimulation in area 5 and recording from area 7 (see Fig. 2). Reciprocal corticothalamic connections were demonstrated by CL-evoked antidromic plus orthodromic responses in area 5 and orthodromic activation in area 7 (Fig. 1B2). These circuits show intracortical connections, eventually impinging on thalamic neurons (Fig. 1B3).

Figure 2 shows the cellular activity during the slow oscillation under ketamine-xylazine anesthesia. As shown in Figs. 4 and 5, seizures spontaneously developed from this sleeplike oscillation. In the dual simultaneous intracellular recording from areas 5 and 7 (Fig. 2A), the activity was well synchronized despite the 10-mm distance between the two neurons. In response to repetitive (10 Hz) stimuli applied to area 5, the area 5 neuron (in the vicinity of the stimulating electrode) showed large excitatory postsynaptic potentials (EPSPs) that consistently gave rise to two or more action potentials (Fig. 2, Ba and Cu). The latency of cortically elicited spikes increased by 6 ms when comparing the primary responses to the first stimuli (●) to secondary

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**Figure 1.** Experimental paradigm. A: schematic drawing indicating the location of recording and stimulating electrodes. Intracellular recordings from suprasylvian areas 5 and 7 were performed in conjunction with field potential recordings from the vicinity of micropipettes and from the central lateral (CL) thalamic nucleus. Stimulation was applied to areas 5 and 7. A microsyringe containing bicuculline was inserted in the rostral part of area 5. B: cortical and CL thalamic stimulation demonstrate interactions between area 5, area 7, and CL. B1: stimulus to area 7 (●) evoked monosynaptic excitatory postsynaptic potential (EPSP) in area 5 neuron and short-latency excitation (focal negativity) in the CL field potential. B2: CL stimulation (▲) resulted in antidromic activation of area 5 neuron and short-latency excitation in field potential from area 7. Three superimposed traces in each case. B3: corticothalamic circuit inferred from above data and indicating that cortico-CL neuron in area 5 receives monosynaptic projections from area 7.
responses evoked by later stimuli (**). This was due to a progressive elongation of the underlying EPSPs. The correlation between latency and stimulus number in the pulse train gave a Pearson correlation coefficient of 0.85. The progressively increased latency is characteristic for cortical augmenting responses to repetitive stimuli at frequencies between 5 and 15 Hz (Castro-Alamancos and Connors 1996; Morin and Steriade 1981; Nuñez et al. 1993). In the neuron recorded in area 7, the EPSPs evoked by area 5 stimulation were elicited with a constant latency (~2 ms later than the 1st action potential in area 5 neuron; Fig. 2, Bb and Cb).

Initiation and synchronization of paroxysmal activity

In all 1,530 recorded seizures, the paroxysmal activity first appeared focally in the cortex. To study the evolution of intracortical and corticothalamic synchrony, we analyzed field potential recordings in 26 animals from 3 reciprocally interconnected regions: cortical areas 5 and 7, and thalamic CL nucleus. The CL nucleus was chosen as a preferred site for recording because of its widespread connections with cortex (see Steriade et al. 1997), which may be implicated in the synchronization of seizures. A spontaneous SW seizure in these cortical and thalamic structures is shown in Fig. 3 (top panel). The paroxysmal activity first appeared in area 7 (period 1). Sequential cross-correlations between cortical and thalamic activities showed a stabilization of intracortical time lags and a concurrent increase in peak amplitude of the intracortical synchrony during period 2 (Fig. 3, thick line, middle panel). Eventually, during period 3, time lags stabilized and a concurrent increase in peak amplitudes occurred within corticothalamic activities. During most of period 3, the time relations between the signals remained constant, and the amplitude of cross-correlation functions remained high until the paroxysmal activity ended (it first ended in area 7, where it initially started). The wave-triggered averages in Fig. 3 (bottom 3 panels) similarly show that, initially (1), the depth negativity in area 7 was not reflected in any other lead. In 2, there was an associated negativity in area 5, indicating that this cortical area participated in the seizure, at a time when the related thalamic CL nucleus did not yet show synchronous activity. In 3, there were synchronized paroxysmal negativities not only in areas 7 and 5 but also in the activity recorded from the CL nucleus. The increased intracortical synchrony during a seizure, established well before related thalamic nuclei were entrained, was a general finding in our analyses.

Relations between intracellular activity and field potentials during spontaneous seizures

Intracellular recordings were performed simultaneously with field electroencephalogram (EEG) potentials from the surface and depth of adjacent and/or distant cortical areas. This demonstrated that changes in cellular activity patterns often preceded overt EEG seizure activity (Fig. 4). The duration of the depolarizing component of the slow oscillation during the epoch preceding the seizure became progressively longer, and, accordingly, most neurons increased the number of spikes per depolarizing phase when approaching the onset of seizure (Fig. 4, compare details in A with B). The shape of the action potentials and fast afterhyperpolarizations (fAHPs) remained unchanged until the seizure became apparent at the EEG level (Fig. 4C). Thereafter, a broadening of action potentials and a gradual decrease in amplitudes of fAHPs were observed. The fAHP in area 5 neuron illustrated in Fig. 4 had a large amplitude (12 mV) and a short duration (0.6 ms at half-amplitude) during the slow oscillation and the initial part of the seizure. Only during the high-frequency spike bursts related to the fast component of seizure, coinciding with decremental spike amplitude, did the fAHP disappear (Fig. 4D). The electrophysiological properties of this cell, namely, high-frequency (300–600 Hz) spike bursts, with very short duration of action potentials (0.25 ms at half-amplitude), pronounced fAHPs, depolarizing afterpotentials (DAPs), and succession of spike bursts during all fast components of seizure, are similar with the pattern described in Fig. 7 of the previous paper (Steriade et al. 1998a). This pattern characterizes fast-rhythmic-bursting (FRB) neurons, as identified by depolarizing current pulses (Fig. 7B of Steriade et al. 1998a; see also Gray and McCormick 1996; Steriade 1997; Steriade et al. 1998b).

In the initial part of seizures, 164 of 221 recorded neurons showed progressively increased hyperpolarizations between the depolarizing components (Figs. 4 and 5). Moreover, in some neurons this feature could be more pronounced than the increased amplitude of the depolarization (Fig. 4).

Synchronization of cortical cells during the slow oscillation and spontaneous seizures

The time delays between corresponding events in simultaneously recorded cortical neurons were reduced during spontaneously occurring seizures, as compared with the preceding epochs of slow oscillation. The range of values observed during seizures had decreased variability, as well as a central tendency (mode, median, mean) closer to zero. This was most pronounced for the 3-Hz SW component and fast runs of seizures. In Fig. 5, the area 5 neuron preceded the area 7 neuron in 178 of 182 depolarizing complexes, including those measured during the prior epoch of slow oscillation. The depolarizations in area 5 neuron had larger amplitudes and steeper slopes, and the cell displayed partial spike inacti-
FIG. 3. Spontaneous spike-wave (SW) seizures first appeared in neocortical areas and spread intracortically before related thalamic nuclei were entrained. Depth-electroencephalograms (EEGs) from areas 7 and 5, and electrothalamogram (EThG) from the intralaminar CL nucleus during a spontaneously occurring seizure (top panel). A: expanded detail of the period marked A in the left panel. Middle panel: sequential cross-correlation of 500-ms windows from periods marked 1–3; peak amplitude on left ordinate; displacement of this peak from time 0 of the cross-correlation function (right ordinate; see calibration bar from 0 to 250 ms). Thick lines represent the cross-correlation of area 7 with area 5 (A7 x A5), thin line area 7 with thalamus (A7 x Th), and dotted line area 5 with thalamus (A5 x Th). The wave-triggered averages (n = 12) were taken from the period marked 1, 2, and 3, respectively (bottom 3 panels). The spiky negativity of SW complexes, immediately following a wave in area 7, was used as reference time.

Compared with the time lags measured during the slow oscillation, before seizure, the time lags between the two simultaneously recorded areas 5 and 7 neurons were significantly smaller during both low-frequency SW complexes (1–2 Hz; P < 0.01) and faster SW complexes (3 Hz; P < 0.00001). In Fig. 5, the median time lags between areas 5 and 7 neurons were 72.5 ms during the slow oscillation, 40.2 ms during SW complexes at 1–2 Hz, and 27.2 ms during SW complexes at 3 Hz. Time lag differences between SW complexes at 1–2 and 3 Hz were statistically significant (P < 0.0001; all comparisons made using the Mann-Whitney U test).

Corticothalamic synchrony during spontaneous SW seizures

To further study the cellular correlates of intracortical and corticothalamic synchrony during seizures, we performed simultaneous extracellular recordings from neocortical and PG/RE or thalamocortical neurons in four animals. The example in Fig. 6 is typical for these results and shows a spontaneous seizure recorded from cortical areas 17 and 18 and the analogue of the thalamic RE nuclear complex in the visual system, the PG nucleus. The PG origin of spike bursts was demonstrated by the long duration and acceleration-deceleration patterns of those neuronal bursts (see details in Steriade et al. 1997). The wave-triggered averages and periwave histograms of unit discharges (reference time was the sharp depth negativity of field potentials from area 18) demonstrated intracortical as well as corticothalamic synchrony during both slow oscillation and spontaneously occurring SW seizure. During the slow oscillation, the wave-triggered average of PG slow waves showed only weak synchrony with the slow oscillation (longer duration of slow-wave complexes, more variable jittering, together leading to less ample average). However, the periwave histogram of PG cell’s discharges demonstrated a periodicity in the cellular firing that was synchronous with the spindle sequence recorded from areas 18 and 17. During the SW seizure, there...
was robust intracortical and cortico-PG synchrony in both field potentials and cellular discharges. The PG cell increased its firing rate in relation to the peak negativity of the field potential from area 18. Thus the number of spikes in the time period from \(-50\) to \(+110\) ms (before and after the peak negativity in the cortical depth) increased from 1.7 during the slow oscillation to 8.3 during the SW seizure, and the average number of spikes per second increased from 14.2 to 29.8.

The increases in firing rate of PG neuron and cortico-PG synchrony contrasted with data obtained by recording thalamocortical (TC) cells during another spontaneous seizure, 4 min later, along the same microelectrode track, this time within the ventrally located LG nucleus (Fig. 7). The area 17 neuron was the same as in Fig. 6. The intracortical changes during the slow oscillation and SW seizure (Fig. 7) were similar to those reported above (Fig. 6). The LG field potential showed synchronization with both the slow oscillation and the SW seizure. However, during the spiky component of SW seizure, the LG neuron decreased its firing rate, compared with the slow oscillation (see firing histogram triggered by depth negativity in area 18). Thus the number of spikes in the time period \(-50\) to \(+110\) ms before and after the peak negativity of cortical field potentials decreased from 1.7 (slow oscillation) to 1.1 (SW seizure).

Taking into consideration the amplitudes of wave-triggered averages and the shapes of histograms in Figs. 6 and 7, we reach the conclusion that PG (RE) neurons were more strongly entrained in paroxysmal activity by corticothalamic projections than TC neurons.

**Altered cortical responses after placement of bicuculline syringe in the cortex**

The changes in cortical responses that resulted from the placement of a syringe with 10 \(\mu\)l of 0.2 mM bicuculline in area 5 are illustrated in Fig. 8. The presence of a bicuculline-
filled syringe induced major changes in cortical field potentials evoked by thalamic LP and cortical area 5 stimulation, despite the fact that no volume was deliberately injected. The amplitudes of evoked responses increased for either thalamic or cortical stimulation. Both the early excitatory (depth-negative) component (peak latency 6 ms) and the secondary component (latency onset at ~25 ms, peak latency at 45–48 ms) increased in amplitude, but the increase was spectacular for the late, multipeaked component. The leads 1–3, closest to the syringe (see brain figure at the bottom of Fig. 8), showed the largest change in response amplitude. 1) In response to thalamic LP stimulation, the primary response grew by a factor of 3 for all leads, whereas the secondary response grew by a factor of 18 in field 1 and a factor of 4 in field 8 (the most distant site from the syringe). 2) In response to area 5 stimulation, the primary response grew by a factor of 6–7 for all leads, whereas the secondary response grew by a factor of 20 in field 1 and a factor of 14 in field 8.

**Intracortical synchrony during bicuculline-induced seizures, as a function of distance between recorded sites**

To study the intracortical synchronization during bicuculline-induced seizures, as a function of distance and of evolution in EEG activity, we used the paradigm illustrated in Fig. 9 (n = 8). After insertion of the syringe between electrodes 1 and 2 in the rostral part of the suprasylvian gyrus, the precursor sign of paroxysmal activity in field potentials (asterisk corresponding to B) was an increased steepness and amplitude of depth-negative waves during the slow oscillation (compare A and B). With time, the paroxysmal field potentials grew in amplitude (C) and started to appear rhythmically, with increasing frequency (D). The intracellu-
lar correlate of field potential illustrated in C is termed paroxysmal depolarizing shift (PDS) (see Steriade et al. 1998a). In six of eight animals, this development culminated in SW or PSW seizures (Fig. 9D). Sequential cross-correlations of representative periods consisting of slow oscillation, recurring PDSs, and SW/PSW seizures showed that the intracortical synchrony was reduced with distance for all these three types of activities. The increases in intracortical synchrony, from slow oscillation to seizure, were of similar magnitude at all interelectrode distances (Fig. 9, bottom panel).

**Dynamic changes in intracortical time lags during paroxysmal activities**

Analyses of time relations between simultaneously recorded cells (n = 48 cell couples) and field potentials (n = 27) showed variations during the course of a seizure. The dynamics of time relations were analyzed as explained in the legend of Fig. 10. The area where the seizure was first apparent is referred to as “site of initiation” and other area(s) as “other(s).” Although during spontaneous seizures the site of initiation had no preferred localization, in the experiments with intracortically leaked bicuculline, the paroxysmal activity always started close to the syringe. Because there were no overt differences in the patterns of spontaneously occurring and bicuculline-induced seizures, we conclude that, in the case of spontaneous paroxysms, the site of initiation was closer to a focus and that those foci were uniformly distributed over the cortex in our database.

For a dual recording, we quantified the following parameters: 1) individual time lag (between a pair of corresponding events); 2) sign (+ or −) of the individual time lag (indicating which site precedes); and the dynamic evolution of these two parameters. Out of the 160 analyzed sei-
FIG. 7. Relations between SW complexes of spontaneously occurring cortical seizure and firing patterns of lateral geniculate (LG) neurons. Same animal as in Fig. 6, recorded 4 min later, after thalamic microelectrode had been moved down, from PG nucleus into the underlying LG nucleus. 

Top panel: surface and depth-EEG from area 18, and 2 extracellular recordings, one from area 17 (same cell as in Fig. 6) and the other representing multiunit LG activity. 

Middle panels: expanded details from slow oscillation (1) and SW seizure (2). 

Bottom panels: wave-triggered averages and periwave spike histograms from slow oscillation and the SW seizure. Reference time was the sharp depth negativity in area 18. The amplitude of the slow waves in the wave-triggered averages were multiplied by 4. Binwidth 40 ms.

zures, in 80% (127 seizures), the sign of the individual time lags alternated throughout the seizure (Fig. 10). In the remaining seizures, the sign of time lags did not change (see Fig. 5). Of particular interest was the time lag at the onset of the seizure (1st PDS). In 60% of the cases (97 seizures), the first PDS at the initiation site preceded the corresponding depolarizing event at the other site (see Fig. 5). In the remaining seizures, the first depolarizing event in the other site preceded the corresponding event at the site close to the focus (Fig. 10). In the latter case, the depolarization at the onset of the seizure could be either a complex of the slow oscillation or, when seizures become recurrent and widespread, a PDS (see below).

The example in Fig. 10 shows a simultaneous dual intracellular recording from areas 5 and 7, in conjunction with depth-EEG from the same areas. Below, the relations between times of maximal slope (highest $\Delta V_m/\Delta t$) at the onset of depolarization in the two recorded neurons are plotted. This demonstrates that the time relations between those two neurons changed continuously, so that they alternated in preceding each other (A and B). Variations of time lags between corresponding events in the course of the same seizure were systematically found in our dual intracellular recordings. During fast runs (bottom right panel in Fig. 10), the amplitude of time lags showed less variations from one cycle to the next than was observed during the epochs with SW complexes at 2–4 Hz. Figure 10 also illustrates that even though the paroxysmal activity was induced by a bicuculline-filled syringe inserted rostrally to area 5 neuron, the cell in the distant area 7 actually preceded the cell in area 5 for most part of the seizure. The area 7 cell also reached the most depolarized membrane potential level (C). That the activity far away from the focal bicuculline diffusion in the rostral part of the suprasylvian gyrus was preceding the ac-
FIG. 8. Changes in depth-cortical field potential evoked by stimulation of the lateral posterior (LP) thalamic nucleus (left panels) and cortical area 5 (right panels) after placement of a syringe with 10 μl 0.2 mM bicuculline in area 5. The bicuculline was not injected, but diffused. Eight electrodes (1.5 mm apart) were inserted, with the syringe between electrodes 1 and 2 (see brain figure). Top panels: averaged responses (n = 30), 2 min after insertion of syringe. Bottom panels: averaged responses (n = 30), 120 min later.

Activity closer to the infusion, at least intermittently, was observed in 90% of seizures (see also Fig. 11).

In some animals (n = 4), the two main components of the seizure (SW complexes at 2–4 Hz and fast runs at 10–15 Hz) seemed to originate in different cortical foci. During the initial part of the seizure depicted in Fig. 11, the most prominent paroxysmal components were recurrent PDSs initiated close to the anterior part of area 5 where the bicuculline syringe was inserted (Cx 1). This was assessed by time relations (bottom panel; see method of calculation in the legend). Later, the seizure became dominated by fast activity (~10 Hz), which first appeared in more posterior suprasylvian leads (Cx 4–8). Because fast seizure activity is associated with neuronal depolarization, the predominant fast field potentials in area 7 (Fig. 11) are congruent with intracellular data shown in the preceding figure (see extreme right part depicting time relations between area 5 and area 7 neurons in Fig. 10).

Role of intracortical and thalamocortical projections in synchronization of bicuculline-induced SW paroxysms

To study the effect of disconnecting intracortical pathways on synchronization of paroxysmal activities, we did complete coronal transections of the suprasylvian gyrus in five animals. Before the transection, the wave-triggered averages performed with reference to the sharp depth negativities in area 7 showed high intracortical synchrony of bicuculline-induced seizures (Fig. 12). Using averages triggered by the focal negativities in the thalamic CL nucleus, the thalamus was only weakly synchronized with
FIG. 9. Intracortical synchrony decreases with distance during bicuculline-induced paroxysmal activity. Progressive changes in cortical activity and synchrony after placement of a syringe with 10 μl 0.2 mM bicuculline in area 5. Bicuculline was not injected, but leaked into cortex. Eight electrodes (1.5 mm apart) were inserted; the syringe was between electrodes 1 and 2 (see brain figure). Left part shows slow oscillation (see detail A). A star marks the 1st paroxysmal EEG “spike” (B). Later, the field potentials became dominated by recurrent EEG spikes that, intracellularly, correspond to paroxysmal depolarizing shifts (PDSs, C), eventually leading to a seizure with a polyspike-wave (PSW) pattern (D). Bottom panel: sequential cross-correlation on 1-s windows between all electrode pairs. Peak amplitude of the cross-correlation function was averaged across all electrode pairs (see interelectrode distance below the abscissa) for each of the 3 10-s periods marked Slow, PDS, and Seizure, and plotted as a function of interelectrode distance. Similar voltage calibration in all panels.

the activity in area 7, but it was better synchronized with the activity in area 5 (Fig. 12). After transection between areas 5 and 7, the average triggered by area 7 activity demonstrated impaired intracortical synchrony; indeed, the negativity in area 5 (that was evident before transection) was no longer observed. By contrast, with averages triggered by thalamic CL activity, synchronous paroxysmal spikes were seen in both areas 5 and 7, thus suggesting that the synchrony may be achieved for brief periods through corticothalamiccortical pathways.

**DISCUSSION**

**Intracortical and corticothalamic synaptic linkages**

The direct connections between areas 7 and 5 are demonstrated by monosynaptic EPSPs in area 5 neurons, with a latency of ~1 ms latency, evoked by area 7 stimuli (see Fig. 1B1). The posterior-to-anterior linkages are reciprocated by direct connections from area 5 to area 7 (Amzica and Steriade 1995b). The evidence that at least part of these linkages are transmitted across the suprasylvian gyrus was shown by abolition of responses after lidocaine inactivation in the middle of the gyrus (Amzica and Steriade 1995b). Morphological studies corroborate these data by showing abundant fiber bundles connecting areas 5 and 7 in the cat suprasylvian gyrus (Avendaño et al. 1988; Grtiner et al. 1974). The connections from area 5 to area 7 can also be inferred from latencies constantly longer by ~2 ms when comparing, during repetitive stimuli at ~10 Hz, the depolarizing responses of the area 5 neuron to those of the simultaneously impaled area 7 neuron (Fig. 2). As to reciprocal corticothalamic connections, they are demonstrated by CL-induced backfiring
FIG. 10. Time relations between intracellularly recorded neurons vary during the course of a bicuculline-induced seizure. Seizure in an animal with a syringe with 10 μl 0.2 mM bicuculline in area 5. Bicuculline was not injected. Top panel: simultaneous dual intracellular recording together with depth-EEG from areas 5 and 7. For each cell and each depolarization complex, we selected the time point of the steepest slope of the membrane potential (highest $\Delta V_m / \Delta t$). We subtracted the time point of area 7 cell from the corresponding time point of area 5 cell, and plotted the resulting time lags along the ordinate as vertical lines from 0, with the time point of area 5 cell along the abscissa (see time calibration, 25 ms, at the extreme right). Period A: the neuron in area 5 clearly precedes the neuron in area 7. This order is reversed in periods B and C. Bottom right panel: event-related average ($n = 100$) of the 2 cells triggered by the time point of area 7 neuron (dotted line) to estimate the relationship between the 2 neurons during the fast runs.

Synchronization of cortical seizures

Previous in vitro studies have reported the characteristics and propagation of epileptic-like depolarizing shifts in cortical slices (Chervin et al. 1988; Wadman and Gutnick 1993). Such synchronized events may represent models for interictal discharges. In humans, neuromagnetic measurements have shown that interictal EEG "spikes" may originate from a single source and distribute with an orderly field pattern and a fixed chronological sequence of discharges (Barth et al. 1984). The preferred pathways and rather stereotyped propagation described in studies of interictal spikes constitute a simpler way of propagation than in the case of complex seizures developing spontaneously from sleep patterns or elicited by small amounts of bicuculline leaked within cortex, as described in the present experiments. In some seizures, the depolarizing events (both normal and paroxysmal) in area 5 neuron preceded the activity of the simultaneously recorded neuron from area 7 (see Fig. 5). And the time lags between discharges in those two cells progressively diminished from the slow oscillation (<1 Hz) before the seizure to paroxysmal epochs characterized by SW complexes at 1–2 Hz and, further, to seizure periods with SW
FIG. 11. Various components of bicuculline-induced paroxysmal activities may be paced from different cortical foci. Top panel: seizure after placement of a syringe with 10 μl 0.2 mM bicuculline in area 5. Bicuculline was not injected. Eight electrodes (1.5 mm apart) were inserted with the syringe 1.5 mm anterior to electrode 1. All electrodes were placed at 0.6 mm depth. The seizure started with a slow SW pattern at ~1 Hz, but rapidly became dominated by fast activity at ~10 Hz. The 1st derivative of each field potential ($\Delta V/\Delta t$) was calculated. For each field potential and each negativity, we selected the time point of the steepest decline of the field potential (most negative ($\Delta V/\Delta t$)). We subtracted the time point of field n (2–8) from the time point of field 1. The resulting 7 time series of time lags are plotted in the bottom panel with the time lag along the ordinate as a line from 0, with the time point of field 1 along the abscissa (see time calibration, 10 ms, at right).

complexes at 3 Hz. By contrast, other seizures displayed more unpredictable patterns of synchronization, namely, alternating periods in which paroxysmal events at the site of initiation seemed to be triggered by the corresponding events in the other site, followed by periods with reversed time lags (Fig. 10). The complexity of such seizures was associated with prevalent PDSs and SW/PSW complexes in area 5, whereas the fast components of seizures were more prominent in area 7 and preceded those in area 5 (Fig. 11).

The synchronization of cortically generated SW/PSW seizures, which is impaired after transections between areas 5 and 7, stands in contrast with the cortical coherence of thalamically generated spindle oscillation that survives deep cuts in the middle of the suprasylvian gyrus (Contreras et al. 1996, 1997). Thus, at variance with the intracortical synchronization underlying both the slow oscillation and the seizures emerging thereof, the quasi-simultaneity of sleep spindles is due to the divergent corticothalamic and intrathalamic connectivities.

Although thalamic neuronal activities are apparently not essential for the development of the two major components of seizures described here, i.e., SW/PSW complexes and fast runs, as they occur in athalamic animals (Steriade and Contreras 1998) and even in small cortical slabs (Timofeev et al. 1998), the thalamus may effectively assist intracortical synchronization processes of this type of seizures. The fact that cortical SW complexes drive GABAergic RE neurons to fire high-frequency spike bursts while, simultaneously, TC cells diminish their firing rates (Figs. 6 and 7) corroborate recent experimental (Steriade and Contreras 1995) and modeling (Lytton et al. 1997) studies showing that an important proportion (~60%) of TC cells are hyperpolarized throughout the cortical SW seizures. Nonetheless, at appropriate hyperpolarized levels, the remaining 40% of TC neurons fire rebound
spike bursts that may contribute to the synchronization of cortical seizures. The CL intralaminar nucleus that receives inputs from, and projects to, distantly located cortical areas may be particularly effective in synchronizing the seizure activity when intracortical linkages are lost (Fig. 12). In view of widespread responses over the suprasylvian gyrus, the LP nucleus is probably also implicated in this process (see the LP-evoked responses in Fig. 8).

Seizures as pathological responses in states of disinhibition

By studying the timing of each excitatory complex (cellular depolarization associated with depth-EEG negativity), we observed that local disinhibition did not create a focus that constantly preceded the seizure activity recorded from other sites. Thus paroxysmal excitatory events in area 7, relatively distant from the site of the bicuculline-filled syringe, could precede the corresponding excitations in area 5, close to the syringe (Fig. 10). Although the neuron recorded intracellularly from area 7 clearly showed paroxysmal activity, the EEG recorded from the same area displayed a pattern close to the slow oscillation for most of the analyzed period. We interpret the epochs during which the activity in area 7 preceded that recorded from area 5 as consisting of pathological responses of the disinhibited area 5 neuron to synchronous discharges of neuronal pools in area 7 during the slow oscillation. Projections from area 7 to area 5 indeed exist (see Fig. 1B1). That slowly oscillating neurons from area 7 precede those from area 5 in a majority of cases (70%) was previously shown (Amzica and Steriade 1995a) and is also illustrated by the cell couple in the top panel of Fig. 2. In sum, seizures may start as abnormally synchronized responses after setting into action excitatory projections onto cortical foci in which inhibitory processes have been partially blocked.

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