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Intracellular Analysis of Relations between the Slow (<1 Hz) Neocortical Oscillation and Other Sleep Rhythms of the Electroencephalogram

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The newly described slow cortical rhythm (≈0.3 Hz), whose depolarizing–hyperpolarizing components are analyzed in the preceding article, is now investigated from the standpoint of its relations with delta (1–4 Hz) and spindle (7–14 Hz) rhythmicity.

Regular-spiking and intrinsically bursting cortical neurons were mostly recorded from association suprasylvian areas 5 and 7; fewer neurons were also recorded from pericruciate motor and posterolateral visual areas. Although most cells were investigated under various anesthetics, a similar slow cortical rhythm was found in animals with brainstem transection at the low- or high-collicular levels. These *cerveau isolé* (isolated forebrain) preparations display the major sleep rhythms of the EEG in the absence of general anesthetics.

In 38% of recorded cortical neurons (n = 105), the slow rhythm was combined with delta oscillation. Both cellular rhythms were phase locked to the slow and delta oscillations in the surface- and depth-recorded EEG. In a group of this cell sample (n = 47), delta activity occurred as stereotyped, clocklike action potentials during the interdepolarization lulls of the slow rhythm. In another neuronal subsample (n = 58), delta events were grouped in sequences superimposed upon the depolarizing envelope of the slow rhythm, with such sequences recurring rhythmically at ≈0.3–0.4 Hz. The associations between the two cellular and EEG rhythms (1–4 Hz and 0.3–0.4 Hz) were quantified by means of autocorrelograms, cross-correlograms, and spike-triggered averages.

In 26% of recorded neurons (n = 72), the slow rhythm was combined with spindle oscillations. Regular-spiking cortical neurons fully reflected the whole frequency range of thalamically generated spindles (7–14 Hz). However, during similar patterns of EEG spindling, intrinsically bursting cells fired grouped action potentials (with intraburst frequencies of 100–200 Hz) at only 2–4 Hz.

The dependence of the slow cortical oscillation upon the thalamus was studied by lesions and stimulation. The slow rhythm survived extensive ipsilateral thalamic destruction by means of electrolytic lesions or kainate-induced loss of perikarya in thalamic nuclei that were input sources to the recorded cortical neurons. To further prevent the possibility of a thalamic role in the genesis of the slow rhythm, through the contralateral thalamocortical systems and callosal projections, we also transected the corpus callosum in thalamically lesioned animals, and still recorded the slow rhythm in cortical neurons. These data indicate that the thalamus is not essentially implicated in the genesis of the slow rhythm. However, thalamocortical and callosal volleys (repeated pulse trains at 10 Hz) were able to alter the cortical rhythm and to transform it into faster oscillations. As a consequence of 10 Hz stimulation, some intrinsically bursting cortical neurons developed a self-sustained activity within the same frequency range and discharge patterns as in the final stage of stimulation.

These results demonstrate that cortical neurons integrate various sleep rhythms as a result of interactions between thalamic and cortical networks. The final article in this series (Steriade et al., 1993b) will describe the novel slow oscillation in reticular thalamic and thalamocortical cells and will discuss the reflection of slow thalamic oscillations back onto cortical neurons.

[Key words: slow rhythm, delta rhythm, spindle rhythm, sleep, EEG, neocortex, thalamus, intracellular recording]

In the first article of this series we described various components building up the slow (<1 Hz) depolarizing–hyperpolarizing oscillation of neocortical cells recorded from different cortical areas (Steriade et al., 1993a). We now analyze the relations between this slow cortical rhythm and other sleep patterns of the EEG. As global EEG activity reflects a variety of oscillations, generated in the thalamus and cerebral cortex, we attempted to study the association between the novel slow rhythm (mainly at ≈0.3 Hz) and the two other sleep patterns within the frequency range of delta waves (1–4 Hz) and spindles (7–14 Hz). The dramatic synchrony between cellular and EEG activities shown in the present article supports the data presented in the preceding article, reporting that 88% of cortical neurons recorded from sensory, motor, and associational areas display the slow oscillation. The fact that the slow neocortical rhythm coexists with the thalamically generated delta and spindle oscillations in both single cortical cells and large neuronal networks is indicative for the importance of traveling influxes in interacting thalamocortical networks. We will show that the slow cortical oscillation survives complete lesions of thalamic peri-

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karya projecting to the recorded cortical areas, but that the thalamus potently modulates the cortical rhythmicity.

Materials and Methods

Data reported in this article resulted from the same experiments on adult cats as presented in the preceding article. Details on different anesthetic agents, stimulation and recording procedures, and criteria for neuronal identification by ortho- and antidromic responses to stimulation of ipsilateral lateroposterior (LP) and rostral intralaminar centrolateral (CL) nuclei as well as to stimulation of homotopic foci in the contralateral cortex can be found in the preceding article (Steriade et al., 1993a). Unless otherwise mentioned, the depicted neurons were recorded under urethane anesthesia.

To rule out the possibility that the slow rhythm is due to a peculiar action of urethane or other anesthetics, in four animals ketamine was initially administered (40 mg/kg, i.m.) and large bilateral electrolytic lesions were performed in the mesencephalic tegmentum, to reproduce Bremer's (1935) *cerveau isolé* (isolated forebrain) preparation displaying spontaneous spindles and slower oscillations in the absence of large doses of different anesthetics. Figure 1 in the preceding article (Steriade et al., 1993a) showed the presence of the slow oscillation in naturally sleeping cats and humans.

In six animals, extensive electrolytic or excitotoxic thalamic lesions, including the pulvinar (PUL)-LP complex, mediodorsal (MD), centrum medianum-parafascicular and CL–paracentral (PC) intralaminar nuclei, ventroposterior (VP), ventroanterior–ventrolateral (VA-VL) complex, as well as other thalamic nuclei, were made before recordings to determine whether the slow oscillation of cortical neurons recorded from areas 5 and 7 is dependent upon thalamic input sources. The chemical lesions were performed by injecting 0.1 μl of a saline solution containing 1% kainic acid at six different sites in the thalamus at anterior plane 10; the animals received, in addition to the usual anesthetics, benzodiazepine (Valium, 2.5 mg/kg). In the same preparations, the corpus callosum was cut with a blunt spatula, at the level of the recorded cortical area. Thus, those recorded cortical cells were deprived of their inputs from both the thalamus and contralateral cortex.

Statistical analyses were performed by using the Brain Wave Systems software. The study of rhythmicity and synchrony between simultaneously recorded cells were based on autocorrelograms, cross-correlograms, and interspike interval histograms (ISIHs). When correlations between spike discharges and electrocorticogram-electrothalamogram (ECoG-EThG) slow waves were to be analyzed, we performed spike-triggered averages (STAs). In the latter case, symmetrical periods of up to 15 sec around the first action potential of the spike train composing the slow cellular oscillation were extracted from slow waves and averaged.

Results

This study is based on the same neuronal sample as the preceding article (Steriade et al., 1993a). Out of 277 cortical cells, 23 were recorded extracellularly and 254 intracellularly in association suprasylvian areas 5 and 7 ($n = 233$), motor pericruciate areas 4 and 6 ($n = 25$), and visual areas 17 and 18 ($n = 19$). The resting membrane potential (V_m) was -70.7 ± 0.6 mV (mean ± SE), spike amplitude was 82.1 ± 0.9 mV, and apparent input resistance was 20.6 ± 0.7 MΩ. The recorded neurons belonged to two classes: regular-spiking (slow- and fast-adapting) and intrinsically bursting cells. The input–output organization of cells was defined by orthodromic and antidromic activation (see Fig. 5*D*), showing that many oscillating neurons were callosal or corticothalamic elements receiving synaptic projections from related thalamic nuclei and from homotopic cortical areas in the contralateral hemisphere.

Urethane and ketamine (the latter supplemented by nitrous oxide or xylazine) induced EEG patterns consisting of prevailing slow and delta rhythms, but spindling was also observed at different stages of anesthesia in 14 out of 50 animals. Under deep barbiturate anesthesia, EEG spindling largely prevailed over EEG delta waves.

Relations between the slow (< 1 Hz) and delta (1–4 Hz) rhythms

The association of slow and delta oscillations in the same cortical cell was observed in 38% of neurons ($n = 105$) recorded from all three types of investigated cortical areas. Two patterns of delta activities are described below: (1) clocklike action potentials fired within the frequency range of 1–4 Hz and occurring *between* the depolarizing phases of the slow rhythm (interdepolarizations lulls), and (2) membrane oscillations within the same delta frequency superimposed on the depolarizing phase of the slow rhythm.

(1) The first pattern of combined (slow and delta) rhythmicities and the EEG correlates of these cellular activities were seen in 47 out of 105 cells displaying the slow and delta oscillations. Figure 1*A* shows that the association between the slow (0.16 Hz) and delta (1.3 Hz) cellular rhythms took place in parallel with enhanced amplitudes of ECoG and EThG slow waves, reflecting the increase in cortical and thalamic synchronization. From short-lasting slow depolarizations, giving occasionally rise to one or a few spikes and separated by long periods of neuronal silence, this cell developed to a state characterized by longer depolarizing envelopes and, between them, spectacularly rhythmic single action potentials at 1.3 Hz.

Further analysis of the slow rhythm in this neuron revealed that the amplitude of action potentials superimposed on the slowly recurring depolarizations was about 20% smaller than that seen during the lulls between the slow depolarizations (Fig. 1*B*). This betrays changes in membrane conductance, due to intrinsic and synaptic factors underlying this slow depolarizing event (see Steriade et al., 1993a). In addition to repetitive EPSPs summed into the long-lasting depolarizing component, isolated IPSPs were observed at a V_m more positive than -70 mV (see asterisk in Fig. 1*B*).

The two (slow and delta) cellular rhythmicities and their relations to the field potentials recorded from the cortex and thalamus were also detected by first- and second-order statistics and STAs.

The autocorrelograms (Fig. 2*A,B*) show multiple major peaks recurring every ≈6 sec, reflecting the slow rhythm at 0.16 Hz, as well as minor peaks every ≈0.75 sec (arrowheads), reflecting the delta rhythm at 1.3 Hz. The smaller amplitude of delta peaks, as compared to those reflecting the slow oscillation, is due to (1) the smaller number of action potentials contributing the thalamically generated delta rhythm, as compared to those building up the slow cortical oscillations, and (2) resetting of the delta oscillation in the cortex by the rhythmic occurrence of the slow rhythm.

The analysis of the interspike interval (ISIH) distribution (Fig. 2*C*) revealed two peaks: (1) an early major mode at ≈0.04–0.12 sec, reflecting the ≈10–20 Hz frequency of spike trains during the depolarizing envelopes, and (2) a late mode at ≈0.7–0.8 sec, reflecting the silence periods between the single action potentials recurring at delta frequency (Fig. 2*C*, arrowhead). That the early mode did not reflect firing at 10–20 Hz due to spindle input from the thalamus is indicated by the presence of similar discharge rates on the depolarizing envelopes in thalamically lesioned animals, in which spindling is abolished (see Figs. 10, 12).

Finally, we averaged ECoG and EThG waves triggered by the first action potential in the depolarizing envelopes (dotted line in Fig. 2*D*). The STA shows that each depolarizing envelope

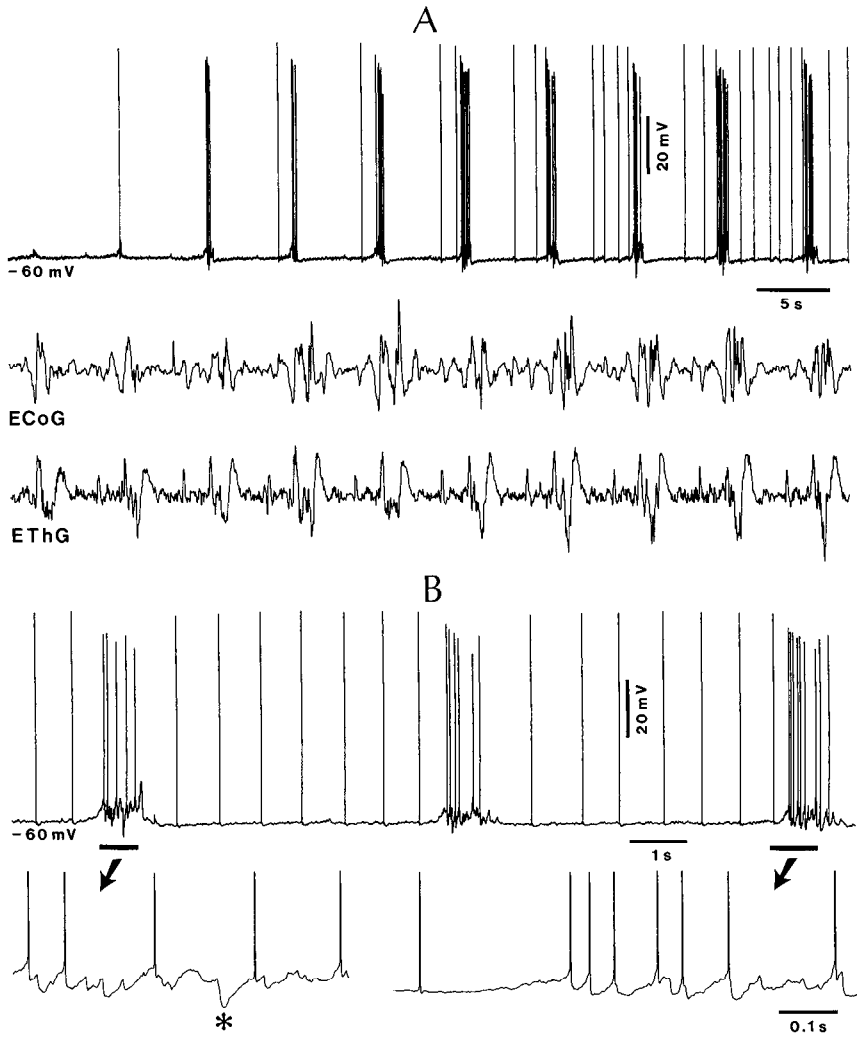

Figure 1. Slow (0.16 Hz) and delta (1.3 Hz) rhythms in regular-spiking, fast-adapting cell recorded at a depth of 0.6 mm in area 5. The neuron was synaptically driven from the LP and CL thalamic nuclei (at latencies of 3 and 2 msec, respectively) and from the contralateral area 5 (at a latency of 12 msec). *A*, Progressive buildup of both slow and delta oscillations with increasing EEG synchronization. Surface ECoG was recorded in area 5, 3 mm rostral to the impaled cell. EThG was recorded from the LP nucleus, through the same electrode that was used to drive the cell. Note the close relation between the slow cellular rhythm and the slow rhythm of ECoG and EThG wave complexes. *B*, Same cell, with fully developed slow and delta rhythms during later EEG-synchronized epoch. Periods marked by *horizontal bars* are expanded *below* (spikes are truncated) to show the details of repetitive spikes during the depolarizing envelopes and some IPSPs (*asterisk*). In this and following similar figures, resting V_m is indicated.

recurring with the slow rhythm (0.16 Hz) is coincident with a complex of EEG waves, starting with a sharp deflection and followed at ≈0.3–0.4 sec by a sequence of spindle waves at ≈10 Hz. Between the depolarizing envelopes, EEG delta waves are visible (arrowheads in middle trace of Fig. 2*D*), recurring at the same rhythm (1.3 Hz) as the stereotyped, periodic single action potentials depicted in Figure 1.

(2) The grouped delta events recurring with a slow rhythm were observed in 55% of the 105 cell sample. Phasic depolarizations and action potentials, occurring within a frequency range of 3–4 Hz, were superimposed on slow depolarizing envelopes recurring with the slow (0.3–0.4 Hz) rhythm (Fig. 3*A*). In a few cells (n = 5), we recorded similar events with QX-314–filled pipettes and observed that depolarizing waves, with an amplitude of ≈15 mV, a duration of 50–100 msec, and a frequency of 2–3 Hz, grouped in sequences repeating every 3–4 sec, survived the blockage of full Na^+ spikes (data not shown).

In addition to intracellular recordings of regular-spiking neurons, as depicted in Figure 3*A*, we observed the same association of slow and delta rhythms in extracellular recordings. The discharge pattern of the neuron depicted in Figure 3*B* suggests its intrinsically bursting nature (see below intracellular recordings of similar bursting cells). The delta (3–4 Hz) oscillations of spike bursts, grouped in slowly recurring (0.3–0.4 Hz) sequences, were closely related to similar rhythms in focal waves reflecting activities in a pool of neighboring cortical neurons.

While the aspect of focal waves illustrated in Figure 3*B* points to the summated activity of a neuronal group, synchronously displaying both delta and slow rhythms, this should not be taken as a general rule. With simultaneous extracellular recordings of two cells, both generally displayed the slow rhythm, but in less than half of such double recordings was the delta rhythm synchronously observed. The distribution of interspike intervals in the neuronal couple of Figure 4*A* shows that only cell *b* displayed a late mode (between 0.3 and 0.5 sec), thus suggesting that a delta rhythm (≈2.5 Hz) may be present. This was confirmed by autocorrelation analyses (Fig. 4*B*). Both cells, *a* and *b*, oscillated at 0.2 Hz, as seen from multiple peaks at ≈5 sec, but only cell *b* also exhibited multiple peaks reflecting a delta rhythmicity at 2.5 Hz (see inset). The two cells were synchronized in their slow oscillation (Fig. 4*C*), which was time-related with a similar rhythm of the surface EEG (Fig. 4*D*; compare Fig. 2*D*).

Relations between slow (<1 Hz) and spindle (7–14 Hz) rhythms

Combined spindle and slow rhythms were found in 26% of recorded neurons (n = 72). Both regular-spiking and intrinsically bursting neurons displayed the slow cortical rhythm, but they

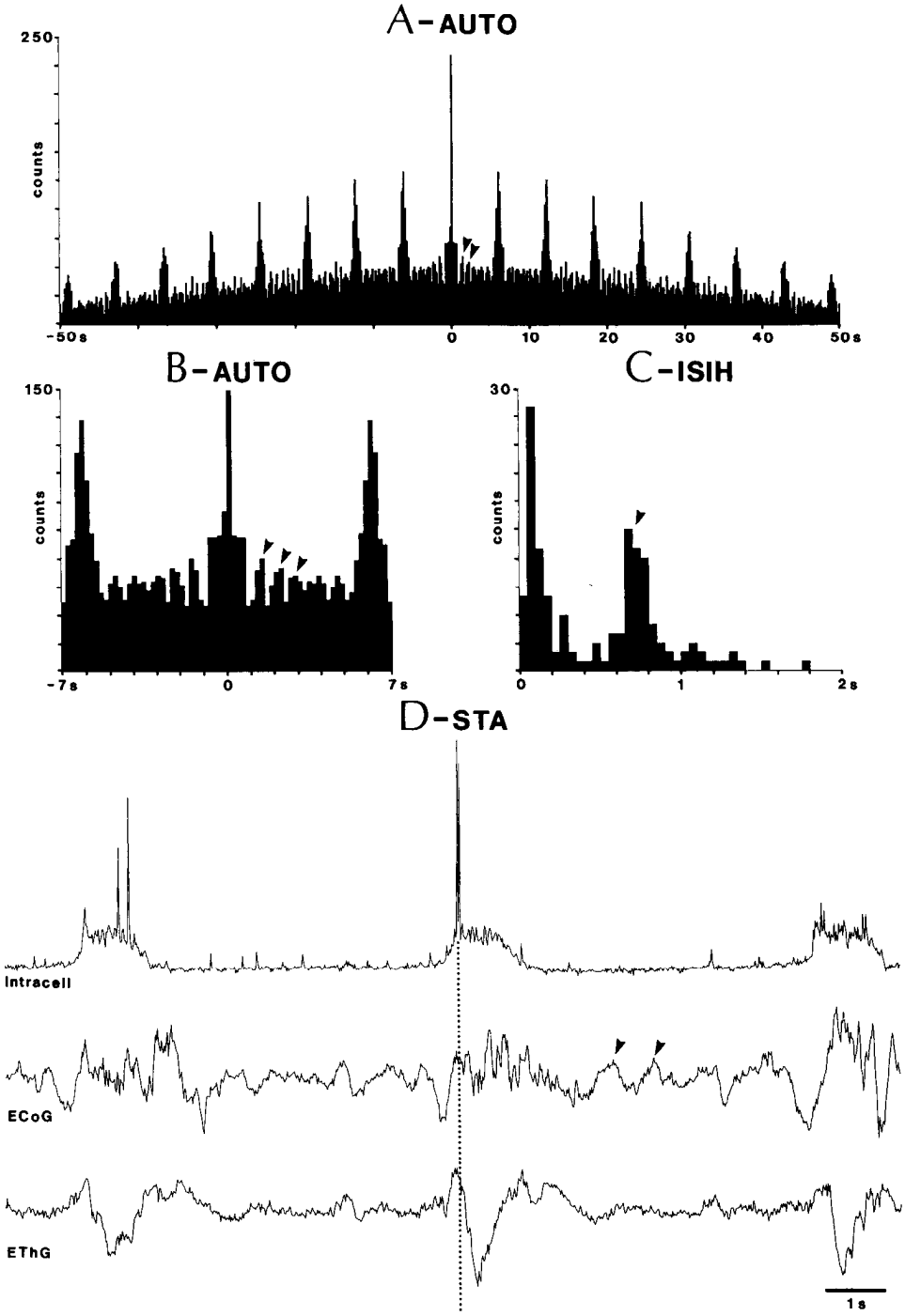

Figure 2. Analyses of slow and delta cellular rhythms related to activity patterns of ECoG and EThG (same cell as in Fig. 1). *A*, Autocorrelogram showing slow rhythm (0.16 Hz) as well as smaller peaks (*two arrowheads*) indicating delta rhythmicity (1.3 Hz) between depolarizing phases of slow rhythm (0.2 sec bin width and 100 sec window). *B*, Detail of *A* to show the delta peaks (*three arrowheads*). *C*, ISIH of cell firing during the analyzed epoch (50 msec bin). The first mode (≈0.1 sec) reflects the ≈10 Hz repetitive discharges during the depolarizing envelopes recurring at the slow rhythm (0.16 Hz), while the second mode (≈0.7–0.8 sec, *arrowhead*) reflects the delta rhythm (1.6 Hz) of single spikes between the slowly recurring depolarizing envelopes (see the original recordings in Fig. 1*B*). *D*, STA over a time period of 15 sec centered around the first action potential occurring during the slow rhythm of depolarizing envelopes (*dotted line*). The averaged intracellular trace ($n = 15$) is depicted with the averaged ipsilateral ECoG and ipsilateral EThG from the LP nucleus. Note three sequences of slow rhythm, spindle waves (≈7–8 Hz) following the initial event of the slow rhythm, and delta waves (≈1.3 Hz, two of them marked by *arrowheads*) between the slow rhythm.

had a differential propensity to follow the rhythmically synchronized spindle oscillations, known to be generated in the thalamus (see Steriade et al., 1990b).

(1) Regular-spiking cells ($n = 58$) exhibited the slow rhythm and also fully reflected the rhythm of thalamic spindles. The corticothalamic cell recipient of thalamocortical inputs depicted in Figure 5 (see *D* for physiological identification) oscillated with slowly recurring prolonged depolarizations, in close temporal relation with a similar rhythm of the EEG (Fig. 5*A*). Embryos of spindling were already visible at this stage of anesthesia on the top of some surface-positive EEG waves. A change in the EEG pattern (Fig. 5*B,C*) was associated with a diminished duration of cellular depolarizing envelopes and a reduction of the superimposed discharges. At this point, steady hyperpolarizing currents blocked the majority of action potentials associated with the slow (0.2 Hz) depolarizations and revealed the spindle rhythm at 10–11 Hz. The amplitude of cellular spindle waves significantly increased toward the middle of the depolarizing envelopes when they reached ≈10 mV, each of them lasting for ≈40 msec (see inset in Fig. 5*C*).

(2) By contrast, intrinsically bursting neurons ($n = 14$), as identified by their burst responses to depolarizing current pulses (see Discussion), could not follow the spindle rhythmicity in its full extent. In spite of an EEG pattern demonstrating the clear presence of cortical spindles, grouped in slowly recurring sequences, the discharges of bursting neurons were only related

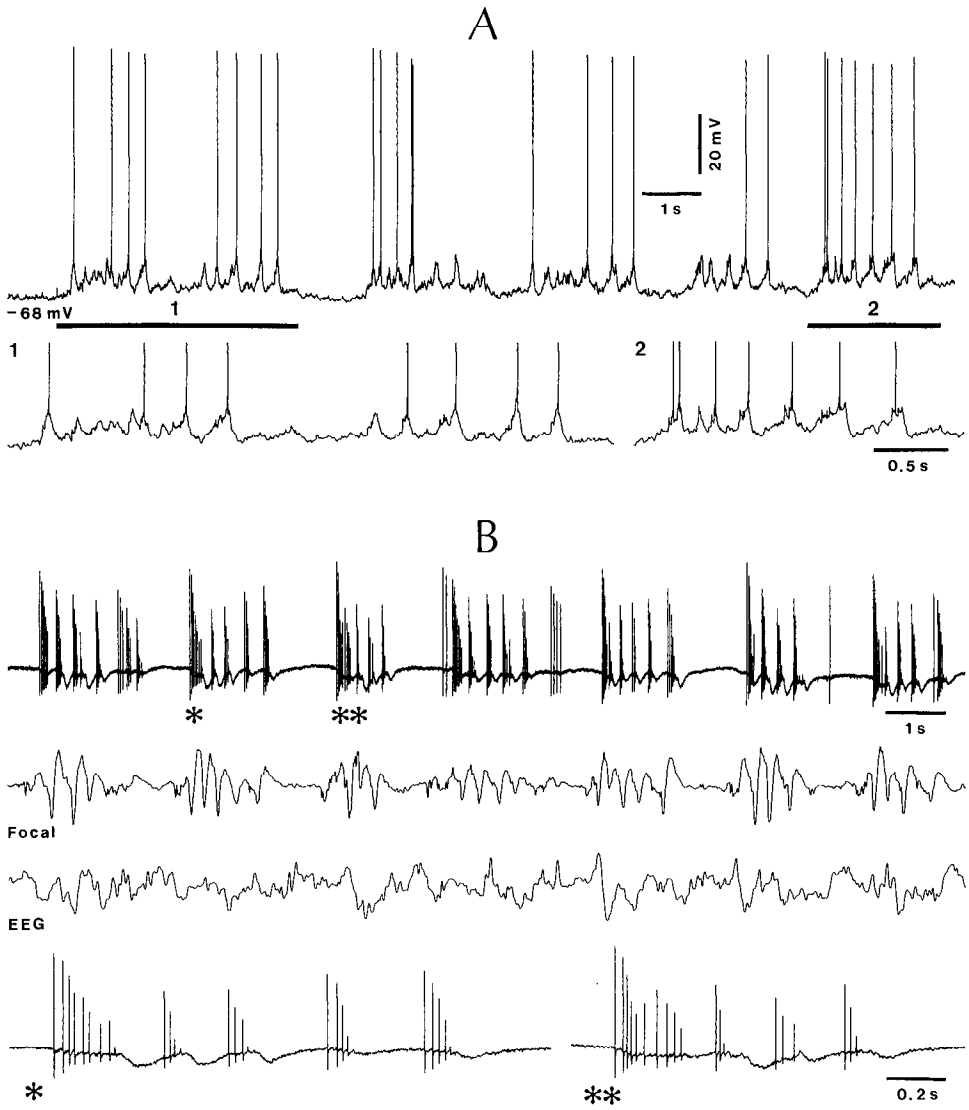

Figure 3. Delta (3–4 Hz) cellular oscillations grouped within sequences recurring with a slow (0.3–0.4 Hz) rhythm. *A*, Intracellular recording of a regular-spiking, slow-adapting neuron at a depth of 0.8 mm in area 5, driven synaptically from LP thalamic nucleus and backfired (3.5 msec latency) from the CL intralaminar thalamic nucleus. Parts marked by *horizontal bars* (*1, 2*) in the *upper trace* are expanded *below*. *B*, Extracellular recording of a bursting neuron at 0.6 mm in area 7, convergently excited by LP and CL thalamic nuclei. Below the cellular trace, focal waves recorded through the same micropipette and gross EEG waves recorded from the cortical surface are depicted. The sequence of spike bursts marked by *one* and *two asterisks* are expanded *below*.

to the slow rhythm, but did not follow the 7–14 Hz rhythm of spindles. During EEG spindle sequences, the neuron in Figure 6 oscillated with repetitive (≈30 Hz) spikes eventually leading to well-formed spike bursts at >100 Hz, but the frequency of such groups of discharges did not exceed 2 Hz.

A similar aspect was seen in intrinsically bursting cells recorded under deep barbiturate anesthesia. Several EEG and cellular phenomena distinguished this type of anesthesia from those described until now (urethane and ketamine). First, spindling was overwhelming (Fig. 7*A*), even more so than in the isolated forebrain, a preparation characterized for its propensity to spindling (see below, Fig. 9). Between sequences of spindle waves recurring with a slow rhythm (0.1–0.2 Hz), waves at the upper range of delta or even higher were observed, but their amplitudes were not as high as those of spindles (Fig. 7*A*). Second, the thalamic and cortical synchrony of EEG spindle sequences was spectacular. This was seen between the thalamus and ipsilateral cortex, but also with the contralateral cortex (see the exception of a nonsynchronous spindle sequence in the contralateral cortex in Fig. 7*A*, open arrow). Third, under barbiturate anesthesia, we never recorded cellular activities within the frequency of delta waves, such as the stereotyped action potentials illustrated in Figure 1. In these conditions, regular-spiking cells faithfully followed the frequency of thalamic spindles (see Fig. 6.20 in Steriade et al., 1990b). At variance, intrinsically bursting neurons (Fig. 7) oscillated at frequencies much lower (4–6 Hz) than the rhythm of the simultaneously recorded EEG spindle (≈12–13 Hz). The intraburst frequency in these two cells was ≈150–200 Hz (see expanded records in Fig. 7*A,B*). The rhythm of cellular oscillation was lower than the frequency of EEG spindle waves even when the cells did not discharge spike bursts, but single spikes (Fig. $7A_2$,*B*), and even when slight hyperpolarization blocked spike firing and only subthreshold spindle oscillations were recorded (see cellular spindle sequence at 6 Hz, extreme right in Fig. $7A_1$, compared to EEG spindles at 12–13 Hz).

As mentioned above, the slow rhythm was predominant during urethane anesthesia, whereas spindle oscillations occurred more infrequently in this experimental condition. Administration of small doses (0.5–2 mg/kg, i.v.) of a short-acting barbiturate in a urethane-anesthetized animal produced an EEG change, from the slow rhythm (0.3 Hz) to sequences of fast spindles recurring with a rhythm of 0.6 Hz (Fig. 8). Correlatively, the intracellular recording showed that the prolonged

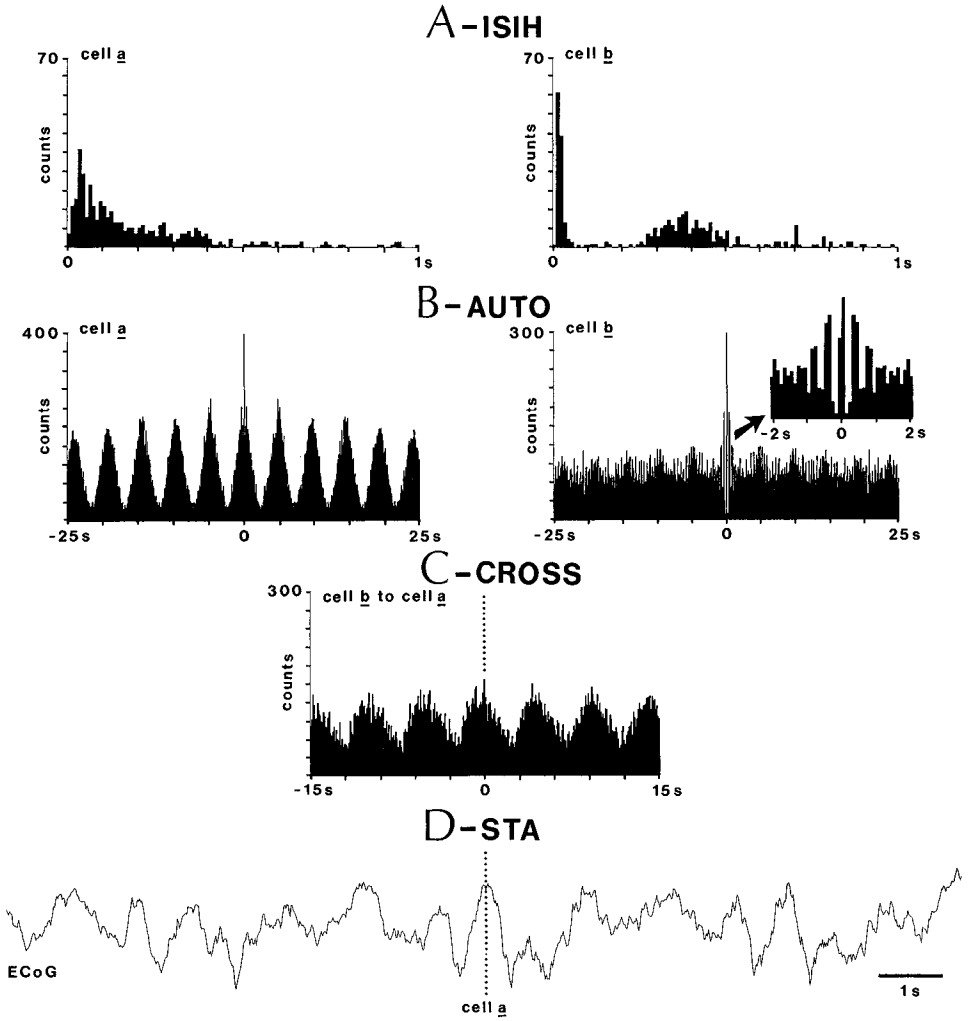

Figure 4. Slow and delta rhythms in two simultaneously (extracellularly) recorded neurons at 1.3 mm in motor area 4: single-spike discharging cell *a* and bursting cell *b*. *A*, ISIHs with 10 msec bins. Cell *b* displayed, in addition to the early mode of short intervals reflecting the intraburst intervals, a late mode between 0.3 and 0.5 sec reflecting the grouped spikes within the delta frequency (≈2.5 Hz). *B*, Autocorrelograms (0.1 sec bin width and 50 sec window) showing the slow rhythm (0.2 Hz) in both cells. The delta rhythm (2.5 Hz) within the slowly (0.2 Hz) recurring discharge sequences in cell *b* is depicted in the expanded *inset* (*arrow*). *C*, Crosscorrclograms showing the synchrony between the two cells (cell *a* taken as reference; 0.1 sec bins and 30 sec window). *D*, STA between the initial action potential in the discharge train of cell *a* and ipsilateral ECoG.

(≈1–1.5 sec) depolarizing envelopes constituting the slow rhythm under urethane developed into faster recurring (0.6 Hz) depolarizations, with much shorter duration (≈0.4 sec).

Intracellular recordings in isolated forebrain preparations

The possibility that urethane produces a slow rhythm that could not be otherwise detected, such as during natural EEG-synchronized sleep, was investigated by intracellular recordings of cortical cells in a brainstem-transected preparation that does not require large doses of anesthetics. It is known that full somatosensory deafferentation is produced by a cut rostral to the pontine site of trigeminal nerve's entrance. The best preparation exhibiting EEG synchronization with large-amplitude waves within the frequency range of different sleep oscillations is the animal with a transection at the low- or high-collicular level (Bremer, 1935). The EEG pattern depicted in Figure 9 is indicative of spindles (≈9 Hz) and delta (≈1–2 Hz) and slow (≈0.3 Hz) rhythms, similarly to the bioelectrical activity recorded during natural sleep. Out of 18 recorded neurons in *cerveau isolé* preparations, 13 displayed the slow rhythm (Fig. 9), that is, a proportion similar to that found in deeply anesthetized animals.

The slow cortical rhythm survives extensive thalamic lesions

To determine whether or not the slow rhythm of cortical association neurons is critically dependent on the thalamus, we made extensive electrolytic or kainate-induced lesions of thalamic nuclei known to project to areas 5 and 7, that is, the PUL-LP complex, intralaminar CL-PC wing, and VA nucleus (see Jones, 1985). The chemical lesion depicted in Figure 10*A*, performed 2 d before the recording session, is a typical example for such experiments. We found a total loss of perikarya and their replacement by a massive gliosis in the PUL-LP, CL-PC, VA-VL and anteromedial–anteroventral (AM-AV) nuclear complexes, as well as ≈80% loss of cells in ventromedial (VM), VP complex, and MD nucleus (Fig. 10A_1–A_4), more than necessary to deprive areas 5 and 7 of their thalamic inputs completely. Since, as shown below, the slow rhythm was still recorded in the neocortex, in three animals we also made callosal sections in the commissural region connecting areas 5 and 7 of both hemispheres (Fig. 10*B*), in order to prevent the possibility that contralateral suprasylvian areas, driven from the thalamus, could induce the slow rhythm.

With recordings of both regular-spiking and intrinsically bursting cortical cells, we were able to demonstrate the presence of the slow rhythm in thalamically disconnected areas 5 and 7 cells (n = 24). (1) In experiments with only thalamic lesions (without callosal cuts), we could identify the recorded cells as projecting to, or receiving direct inputs from, contralateral area 5 or 7. Such neurons oscillated at 0.3–0.4 Hz, identically to those recorded in the intact brain. An example is illustrated in

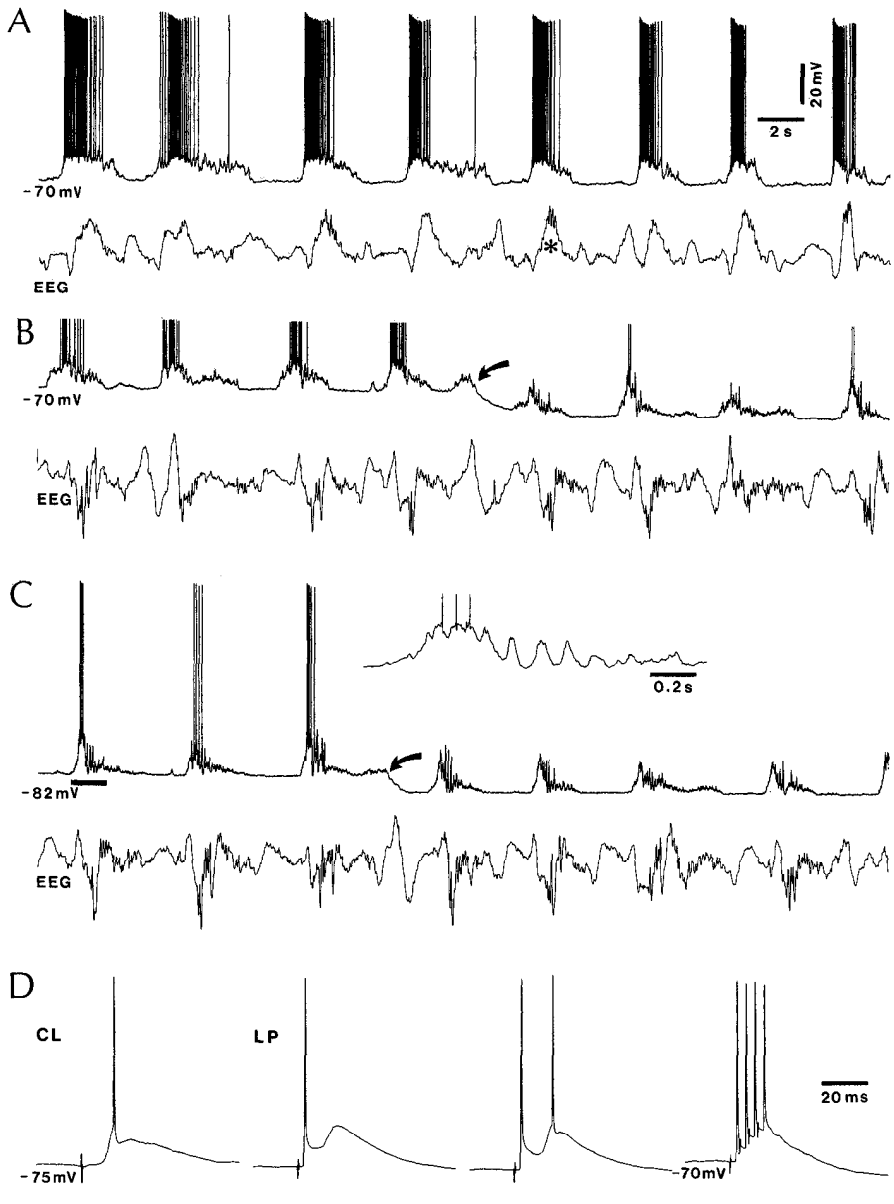

Figure 5. Slow rhythm and spindle oscillation: intracellular recording of regular-spiking, slow-adapting, corticothalamic cell, recorded at 1.5 mm in area 7. *A–C* show cellular activities during increasing EEG synchronization under urethane anesthesia. *Oblique arrows* in *B* and *C* indicate application of steady hyperpolarizing currents (−0.5 nA in *B*, and more −0.4 nA in *C*) to reveal sequences of cellular spindles (≈10–11 Hz) recurring with the slow rhythm (≈0.2 Hz). The intracellular spindle marked by *horizontal line* in *C* is expanded in *inset* (spikes truncated). *D*, Synaptic activation (7.5 msec latency) from CL thalamic nucleus; antidromic discharge (2.2. msec) followed by slow depolarization (peak at 18 msec), occasionally leading to spike discharge, in response to LP thalamic nucleus; and faithful following of fast (≈230 Hz) antidromic LP volleys.

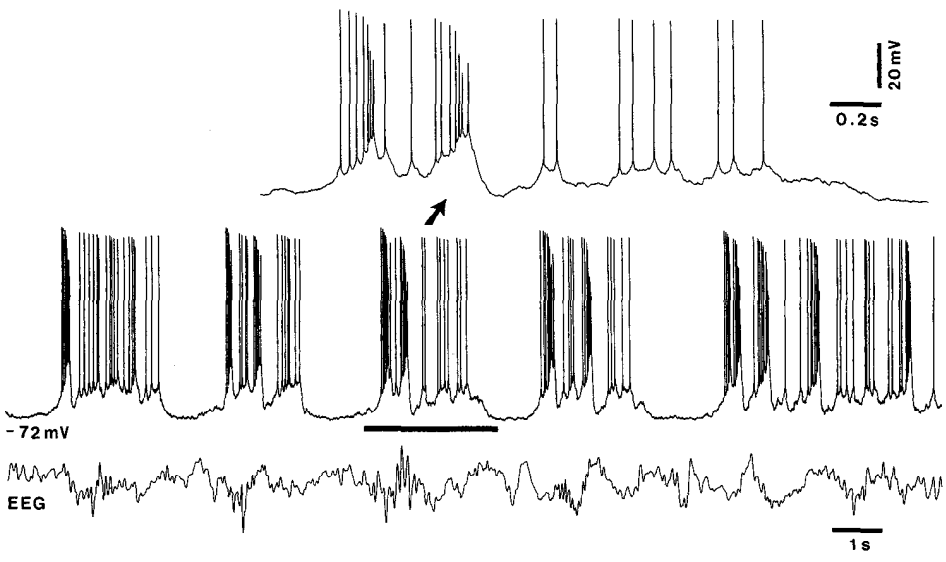

Figure 6. Intrinsically bursting neuron does not follow the frequency of spindle oscillation: area 5 neuron at a depth of 1.3 mm, convergently driven from LP thalamic nucleus and contralateral cortex. Note EEG spindle waves (≈9 Hz) recurring with the slow rhythm (0.3 Hz). The burst sequences occurred in close time relation with the EEG slow rhythm, but the rhythm of cellular bursts was much slower (≈3–4 Hz) than that of spindles. Period marked by *horizontal line* is expanded *above*.

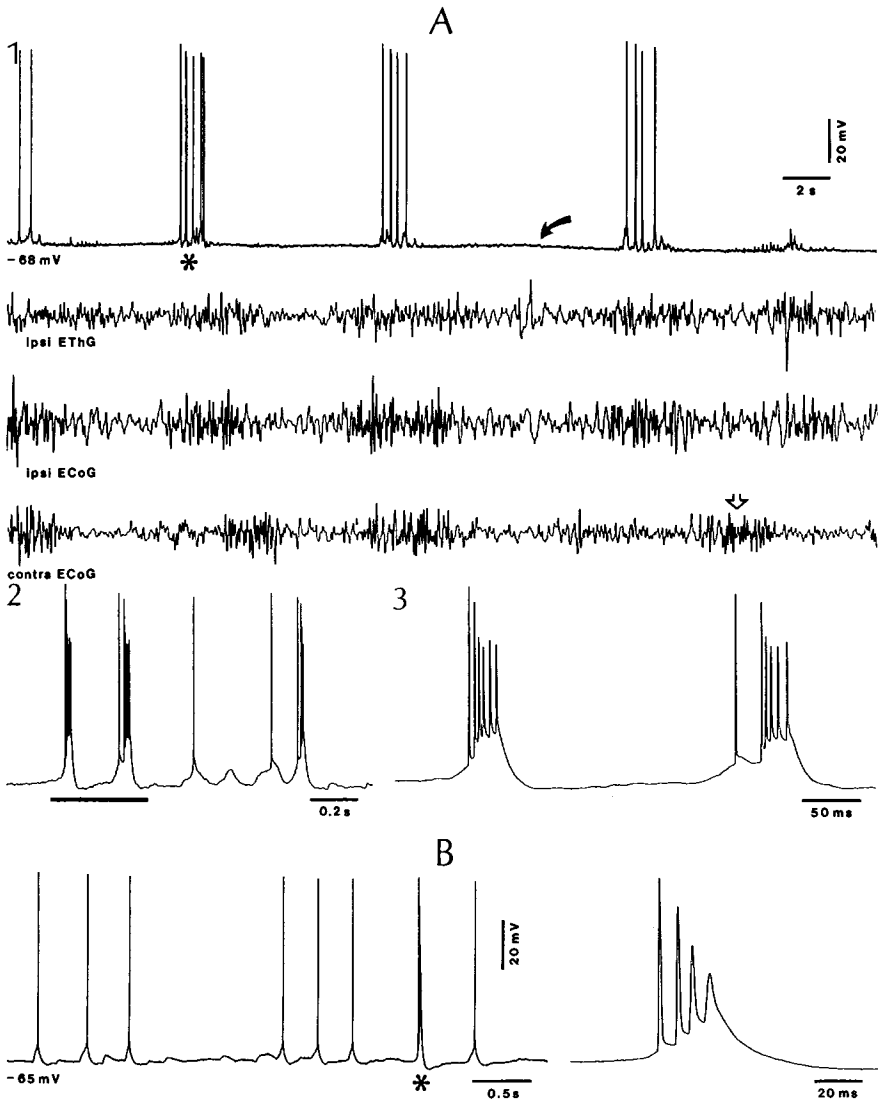

Figure 7. Slow rhythm of barbiturate spindling and associated firing of intrinsically bursting neurons: recordings under deep (35 mg/kg) pentobarbital anesthesia. Two cells were recorded from area 5, at depths of 1 mm (*A*) and 1.5 mm (*B*). *A*, Simultaneous recordings of cellular spindling, ipsilateral EThG from CL intralaminar nucleus, and ipsilateral as well as contralateral ECoGs from area 5. Cellular spindle sequence marked by *asterisk* in *1* is expanded in *2*; part of the spindle in *2* marked by *horizontal line* is further expanded in *3* to show the pattern of spike bursts. Slight DC hyperpolarization in *1* is marked by *oblique arrow*. *Open arrow* on contralateral ECoG trace marks a spindle sequence that was not synchronous with the cell and ipsilateral EThG and ECoG spindling. *B*, A cellular spindle sequence in another cell; burst indicated by *asterisk* is expanded at *right*.

Figure 11*A*, with an intrinsically bursting cell firing stereotyped spike bursts at the onset of rhythmically recurring depolarizations. The bursts generally consisted of five or six action potentials, displaying one or two initial intervals of ≈10–12 msec, eventually leading to high-frequency (160–180 Hz) spikes. The callosally evoked spike bursts rode on a 30–40 msec EPSP (inset in Fig. 11*A*). (2) The slow cortical oscillation survived in animals having, in addition to massive thalamic destruction, callosal cuts disconnecting the right and left association suprasylvian cortices (Fig. 11*B*).

The physiological evidence that thalamocortical systems related to suprasylvian cortical neurons were out of function in these experiments using electrolytic or chemical lesions was provided by the absence of spindling in the cortical EEG. It is known that, after transections of corona radiata disconnecting the cortex from the thalamus (Steriade et al., 1987) or disconnection of thalamocortical cells from the thalamic pacemaking neurons of spindle oscillations (Steriade et al., 1985), cortical spindles are abolished, whereas slower sleep rhythms are preserved. This aspect was also observed in the present experiments with thalamic lesions (Fig. 12*A*). Moreover, administration of a short-acting barbiturate, well known for its potency in inducing spindling, was not followed by cortical spindle oscillations in thalamically lesioned preparations; only slower EEG rhythms were present (Fig. 12*B*). At the cellular level, the effect of barbiturate administration was a change in the duration of rhythmic depolarizing envelopes and, consequently, an alteration in the frequency of the slow oscillation. Before barbiturate administration, the mean duration of cyclic depolarizations was >1 sec and the frequency of slow rhythm was ≈0.3 Hz, whereas 15–20 sec after thiamylal injection the mean duration of depolarizations was <0.5 sec and the frequency of the slow rhythm rose to ≈0.7 Hz (Fig. 12).

Modulation of the slow cortical rhythm by afferent drives: self-sustained changes after thalamic and cortical stimulation

Although the data presented above indicate that the thalamus is not involved in the genesis of the slow cortical rhythmicity, electrical stimulation of appropriate thalamic nuclei induced short- or long-lasting changes in target cortical neurons. As a rule, the slow rhythm was disrupted by thalamic single shocks, inducing long-lasting IPSPs in cortical cells, but this change did not outlast stimulus application (Fig. 13*A*). Much less commonly (n = 3), the slow rhythm (0.3–0.4 Hz) changed its fre-

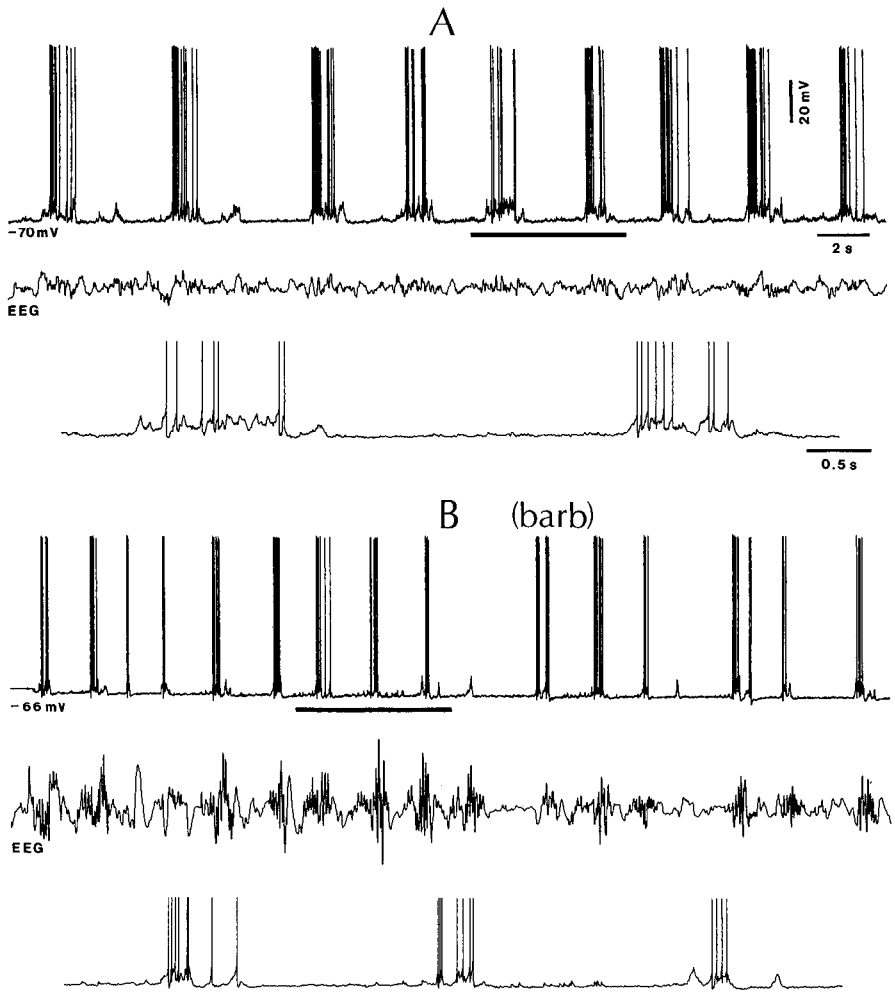

Figure 8. Effect of small dose of short-lasting barbiturate in urethane-anesthetized animal: regular-spiking cell in area 5b (depth 0.5 mm). *A*, Slow rhythm (≈0.3 Hz) of cellular activity during urethane anesthesia. Part indicated by *horizontal line* is expanded *below* (spikes truncated). *B*, Same cell after 2 mg/kg intravenous administration of a short-lasting barbiturate (thiamylal). Part indicated by *horizontal line* is expanded *below* (spikes truncated).

quency to a higher one, within the delta frequency range (1–2 Hz), after repeated trains of thalamic stimuli inducing incremental responses of the augmenting type. Importantly, such a change outlasted thalamic stimulation for 25–40 sec (Fig. 13*B*).

Dramatic changes in cortical rhythmicity, with persistent alterations of cellular activity after the cessation of stimuli, could be induced by repetitive shocks to the contralateral association cortex in thalamically lesioned animals. The intrinsically bursting, layer V cell, recorded from area 7 in an animal with an extensive thalamic lesion (Fig. 14*A*), oscillated at the slow rhythm (0.4 Hz). Stimulation of contralateral area 7 with trains of five shocks at 10 Hz induced augmenting responses, similar to those elicited by thalamic stimulation in a brain-intact preparation. This result is in line with previous data showing that cortical augmenting responses can be elicited by white matter stimulation even after destruction of appropriate thalamic nuclei (Morin and Steriade, 1981; Ferster and Lindström, 1983). The pattern of incremental corticocortical responses changed with the progressive repetition of pulse trains, displaying an increased number of action potentials within each evoked burst on a background of V_m depolarization by ≈7 mV (Fig. 14*B*). After the interruption of cortical stimulation, the neuron discharged *spontaneously* spike bursts at 10–12 Hz (very similar to those evoked in the last period of cortical stimulation), interrupted by long spike bursts recurring with the slow rhythm (0.4 Hz).

Discussion

The variety of cortical sleep oscillations

We have demonstrated that, during states mimicking natural EEG-synchronized sleep, the neocortical electrical activity is characterized by three major types of oscillations within the frequency range of ≈0.3 Hz, 1–4 Hz, and 7–14 Hz. This is valid for animals maintained under deep anesthesia as well as for deafferented, brainstem-transected, undrugged preparations. Parallel studies performed in this laboratory by means of multisite cellular recordings in the neocortex and thalamus of naturally sleeping cats and EEG recordings during human sleep have shown that this variety of oscillations also characterizes the normal behavioral state of quiescent sleep (see also Fig. 1 in Steriade et al., 1993a).

The interest of our findings mainly consists of revealing the diversity of sleep oscillations, with each of different rhythms arising from given intrinsic cellular properties or synaptic mechanisms, but all combined into patterns of activities generated by complex synaptic articulations in intracortical, intrathalamic, and corticothalamocortical networks. Until quite recently, it was assumed, on the basis of incomplete evidence, that the thalamus is the site of genesis of spindle oscillations while the cortex generates delta waves (Steriade et al., 1990b) and the cortical oscillation grouping EEG delta waves with a rhythm at ≈0.3

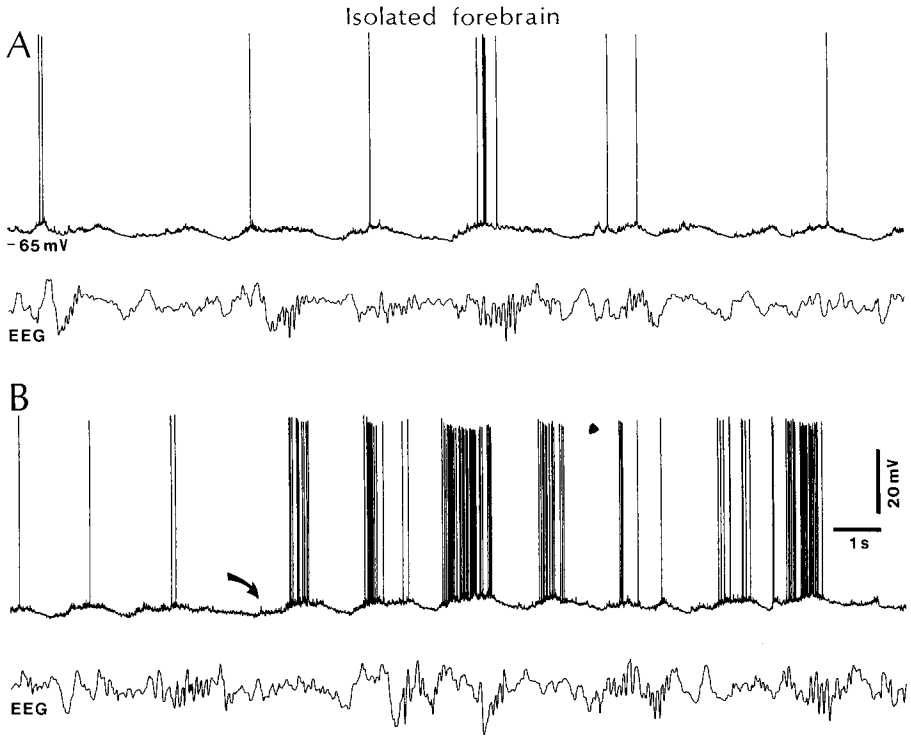

Figure 9. The slow cortical rhythm is present in the undrugged *cerveau isolé* preparation: regular-spiking, slow-adapting cell recorded at a depth of 0.5 mm in area 7. The cellular depolarizing envelopes and the EEG sequences of spindle waves synchronously recurred with the slow rhythm (≈0.4 Hz). *A* and *B* are continuous recordings; slight DC depolarization from resting V_m (−65 mV) was applied in *B* (*oblique arrow*) to show the pattern of neuronal discharges.

Hz was not known. The present set of experimental data provide evidence that, although the intrinsic electrophysiological properties are of fundamental importance for the propensity of single neurons to oscillate (Llinás, 1988), the detailed analysis of neuronal substrates underlying the rhythms distinguishing various states of vigilance can be achieved only by intracellular recordings in a preparation with preserved circuitry, the condition under which billions of elements are interacting as a unity to generate the global electrical activity of the brain.

Interaction between slow and delta oscillations

The common designation of "sleep delta waves" under the frequency range from 0.5 to 4 Hz, as generally used in clinical EEG and experimental studies of brain rhythms, conceals at least two rhythms with different sites of genesis and dissimilar neuronal mechanisms. The intrinsic cellular properties and synaptic mechanisms involved in the genesis of the slow neocortical rhythm (<1 Hz, mainly ≈0.3 Hz) are the topic of the preceding article (Steriade et al., 1993a). The assumption that the slow rhythm is generated within the cortex is substantiated by the present results showing the survival of this oscillation in thalamectomized preparations. The thalamic origin of delta (1–4 Hz) rhythm and the interaction between delta and slow rhythms through thalamocortical circuits are discussed below.

Although delta sleep activity was classically regarded as a rhythm arising in the cerebral cortex because laminar analyses of these waves found vertical sink–source relationships to EEG potentials at various cortical depths (Ball et al., 1977; Petsche et al., 1984), there is now accumulating evidence that delta activity also originates in the thalamus and is transferred to cortical neurons in different layers. Within the cortex, active excitatory–inhibitory synaptic processes and long-lasting intrinsic currents build up the delta waves, as reflected at the cortical surface. Earlier extracellular studies have reported spike bursts within the delta frequency range (2–4 Hz) in VL and dorsal lateral geniculate (dLG) thalamic nuclei (Lamarre et al., 1971; McCarley et al., 1983). Some of these spike bursts could have been delta events. However, it is now known from intracellular studies that such slowly recurring spike bursts may well reflect spindles, not necessarily delta oscillations, because thalamocortical cells do not discharge postinhibitory rebound bursts after each IPSP related to the spindle frequency (7–14 Hz), but only one burst after two, three, or more IPSPs (Roy et al., 1984; Steriade and Llinás, 1988). Besides, at least in the case of VL thalamic nucleus, spike bursts at the same frequency as delta (1–2 Hz) may be the consequence of spike barrages with a similar frequency in afferent neurons recorded from deep cerebellar nuclei (Steriade et al., 1971).

That a stereotyped delta oscillation between 1 and 4 Hz is indeed generated in the thalamus was unambiguously demonstrated in recent intracellular studies of thalamocortical cells recorded from dLG and VP slices (McCormick and Pape, 1990a,b; Leresche et al., 1991; Soltesz et al., 1991) and from a variety of sensory, motor, associational, and intralaminar thalamic nuclei *in vivo* (Steriade et al., 1991; Curró Dossi et al., 1992; Nuñez et al., 1992a). McCormick and Pape (1990a) have proposed a model of delta oscillation resulting from the interplay between two membrane intrinsic currents present in thalamic cells: (1) a hyperpolarization-activated inward (anomalous) rectifier carried by Na^+ and K^+ (I_h) (Pape and McCormick, 1989), and (2) a transient Ca^{2+} current (I_t) underlying the low-threshold spike (LTS) giving rise to bursts of high-frequency, fast Na^+ action potentials (Jahnsen and Llinás, 1984a,b). According to this model, the hyperpolarization of thalamocortical cells activates the I_h, which depolarizes the membrane toward threshold for a Ca^{2+}-dependent LTS crowned by a burst of Na^+ fast spikes; this depolarization inactivates the I_h and the resulting hyperpolarizing overshoot again triggers the I_h, which depolarizes the membrane toward another LTS. The cycle could ideally repeat forever provided that the two processes of I_h–I_t activation–in-

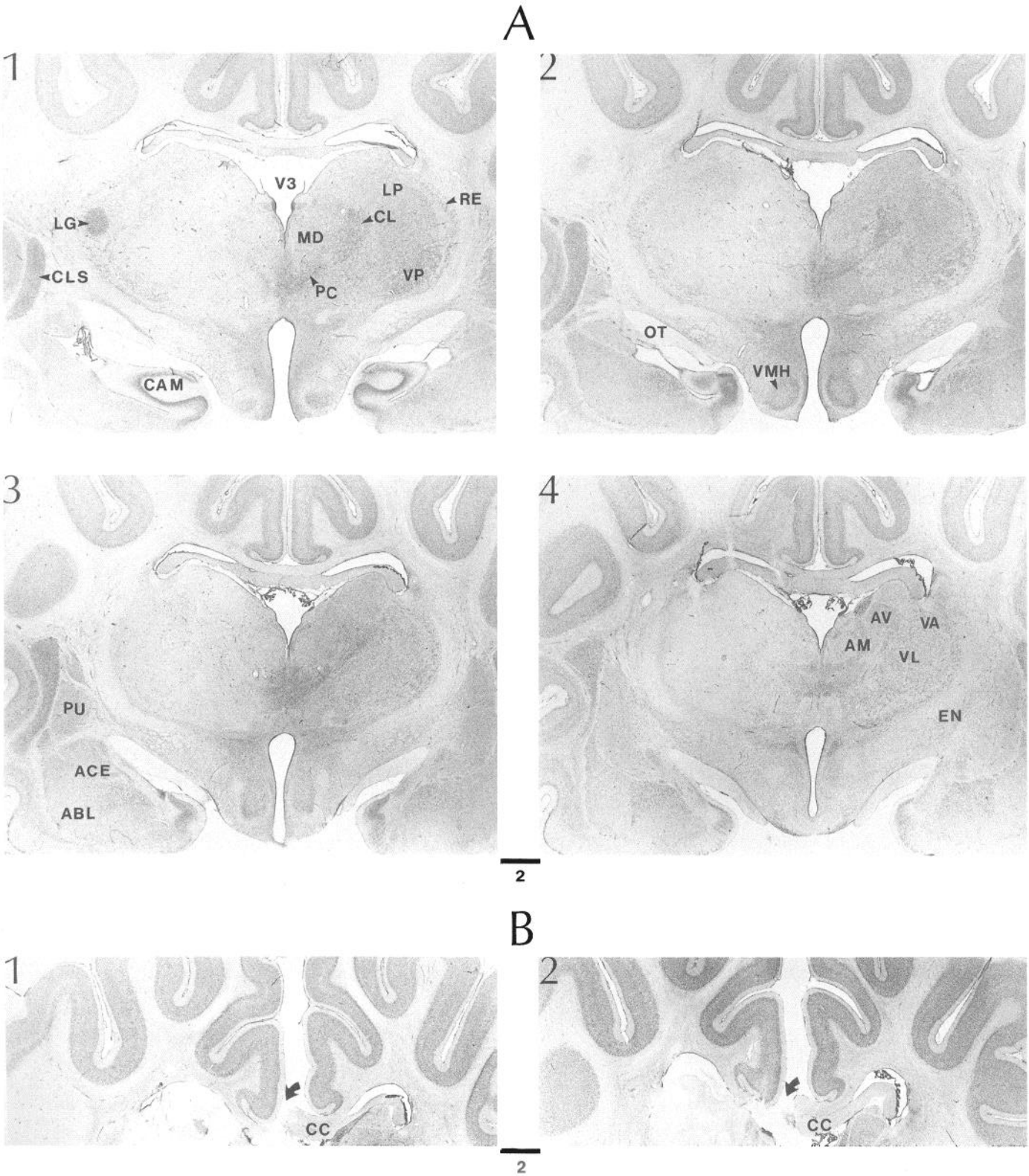

Figure 10. Thalamic lesions and callosal cuts. *A*, Extensive kainic lesion of thalamic perikarya, ipsilateral to recorded cortical neurons displaying the slow rhythm. *1–4*, Four frontal sections (from caudal to rostral). Note three penetrations of the Hamilton syringe through the corpus callosum in *section 4*. *ABL* and *ACE*, basolateral and centrolateral amygdaloid nuclei; *AM* and *AV*, anteromedial and anteroventral thalamic nuclei; *CAM*, corpus Ammoni; *CL*, centrolateral intralaminar thalamic nucleus; *CLS*, claustrum; *EN*, entopeduncular nucleus; *LG*, lateral geniculate nucleus; *LP*, lateroposterior thalamic nucleus; *MD*, mediodorsal thalamic nucleus; *OT*, optic tract; *PC*, paracentral intralaminar thalamic nucleus; *PU*, putamen; *RE*, reticular thalamic nucleus; *VA* and *VL*, ventroanterior and ventrolateral thalamic nuclei; *VMH*, ventromedial nucleus of hypothalamus; *V3*, third ventricle. *B*, Frontal sections showing callosal cuts (*arrows*) at two levels in a cat with extensive electrolytic thalamic lesion. *CC*, corpus callosum. *Horizontal bars* indicate millimeters.

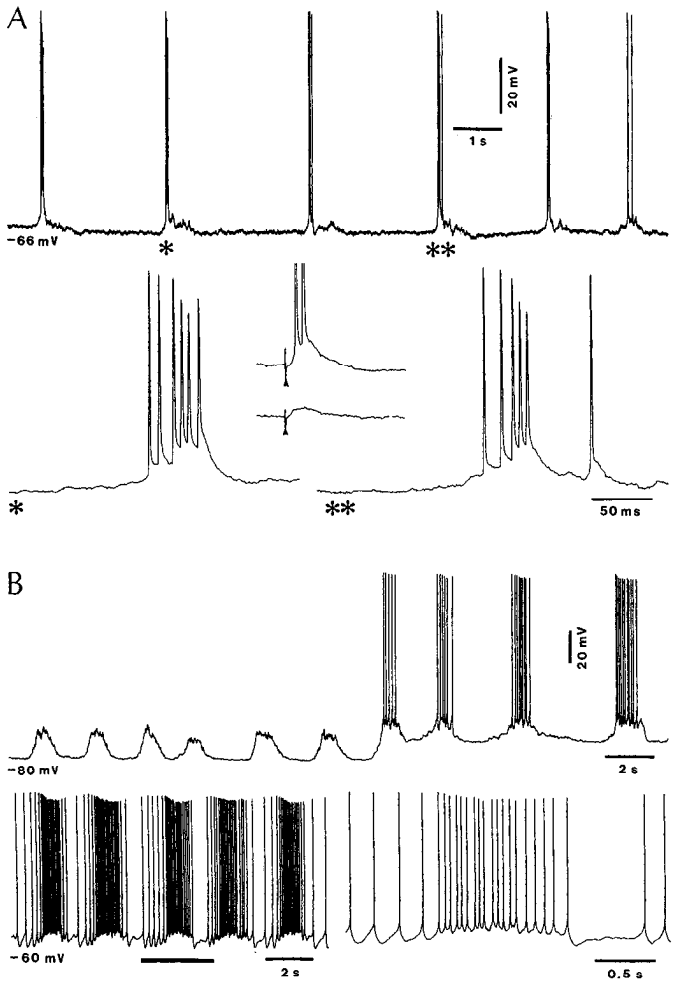

Figure 11. Slow (0.3–0.4 Hz) rhythms of suprasylvian cortical neurons after extensive lesions of thalamic inputs. *A*, Intrinsically bursting cell at 1.1 mm in area 5. Bursts marked by *one* and *two asterisks* are expanded *below*. *Inset*, Spike doublet and, *below*, EPSP elicited by stimulation of contralateral area 5 with decreasing stimulus strengths (*arrowheads*). *B*, Regular-spiking cell at 0.5 mm in area 7. In this animal, corpus callosum was also transected. Rhythmic depolarizing envelopes at the resting V_m (−80 mV) are seen, with action potentials upon DC depolarization (*right part in upper trace*), and further depolarization to −60 mV (*bottom trace*). Part marked by *horizontal bars on bottom trace* is expanded at *right* to show a period (≈0.5 sec) of silenced firing after the repetitive spikes riding on the depolarizing oscillation.

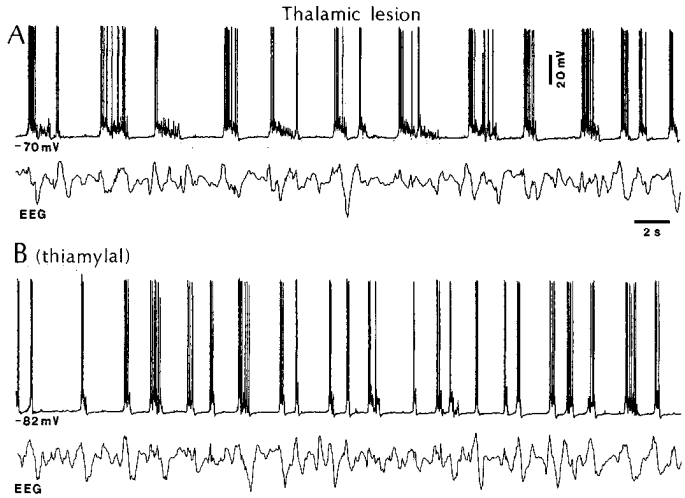

Figure 12. Slow cellular rhythm (0.3 Hz) of area 7 neuron in animal with extensive thalamic lesion and the effect of thiamylal (2.5 mg/kg, i.v.).

activation alternate with one another. The role of voltage-dependent currents in the genesis of thalamic delta oscillation is demonstrated by abolition of this rhythm after administration of I_h and I_t blockers, Cs^+ and Ni^{2+}, respectively (Leresche et al., 1990; McCormick and Pape, 1990a; Soltesz et al., 1991). It is also worth mentioning in this context that, although cortical cells also possess the I_h (Spain et al., 1991), at least in areas 5 and 7 they do not display the intrinsic delta oscillation, because the proportion of cortical association neurons having the I_t underlying the LTS is quite low (10%) and the level of hyperpolarization required to deinactivate this current is around −90 to −100 mV (Nuñez et al., 1993).

Thus, delta oscillation is generated by two currents of thalamocortical cells when their V_m is hyperpolarized by about 10–15 mV. This alteration occurs during natural slow-wave sleep (Hirsch et al., 1983), mainly because of the decrease in firing rates of activating cholinergic and monoaminergic brainstem neurons (reviewed in Steriade and McCarley, 1990). Indeed, the depolarization of thalamic cells by setting into action mesopontine cholinergic neurons (Curró Dossi et al., 1991) leads to blockage of rhythmically recurring LTSs within the frequency range of delta oscillation (Steriade et al., 1991). Another factor leading to the hyperpolarization of thalamic neurons during slow-wave sleep is the decreased firing rates of corticothalamic cells (Steriade, 1978). During waking, the cortical input produces a prolonged depolarization of thalamic cells resulting from a reduction in a resting K^+ conductance, I_{KL}, through the activation of glutamate metabotropic receptors (McCormick and van Krosigk, 1992). After removal of the powerful depolarizing impingement of cortical origin, thalamic neurons are hyperpolarized by about 10 mV and, consequently, spontaneous delta oscillations are seen in virtually all recorded neurons (Curró Dossi et al., 1992).

How are singly oscillating thalamic cells synchronized into neuronal ensembles, and how is it that a stereotyped, clocklike, intrinsic oscillation is transformed into polymorphous, irregular EEG delta waves?

(1) First, although delta is typically an intrinsic oscillation of single neurons, it cannot be reflected at the macroscopic level of the EEG unless thalamic neurons are synchronized (Steriade et al., 1991). This process is mainly achieved through long-range (reticular, RE) or short-range (local-circuit) GABAergic inhibitory thalamic neurons and, in some cases, through synaptic coupling between thalamocortical cells. Both inhibitory (RE and local-circuit) thalamic cellular types can effectively set the V_m of thalamocortical neurons at the required level for the genesis of the hyperpolarization-activated delta rhythm.

The role of RE neurons is indicated by the fact that potentiation and synchronization of thalamic delta rhythmicity may result from stimulation of cortical areas that are not directly related to the recorded thalamic neurons (Steriade et al., 1991). It is known that rostrolateral sectors of the RE nuclear complex are convergently afferented by multiple cortical areas and, in turn, project to widespread thalamic territories (Steriade et al., 1984; Jones, 1985).

As to local-circuit inhibitory thalamic cells, they may be powerfully driven by corticothalamic neurons receiving the rhyth-

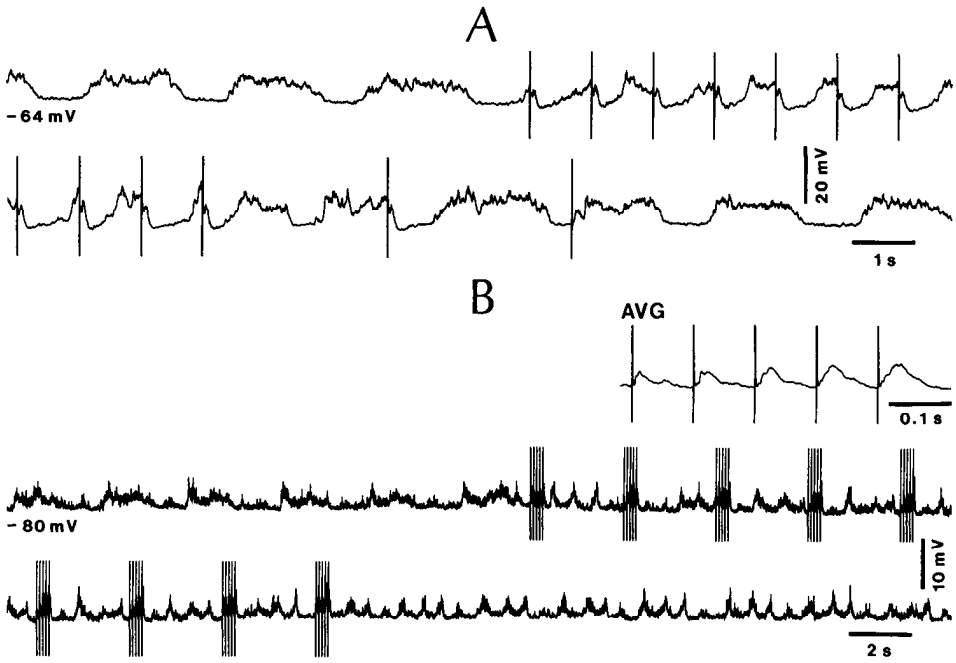

Figure 13. Modification of slow cortical rhythm by thalamic stimulation. *A*, Regular-spiking, corticothalamic cell in area 5 (backfired from CL nucleus), displaying a slow rhythm (0.4 Hz) consisting of depolarizing–hyperpolarizing sequences. The rhythm was disrupted by 1/sec single-shock stimulation of LP thalamic nucleus (*right part in upper trace* and *left part in bottom trace*). Each LP stimulus gave rise to a long-lasting (≈0.5 sec) IPSP. After two LP stimuli separated by 3 sec, LP stimulation was interrupted and the slow rhythm resumed with the previous frequency at 0.4 Hz (*bottom trace*). *B*, Regular-spiking neuron in area 5, with slow depolarizing envelopes recurring at 0.4 Hz. LP thalamic repetitive stimulation [five-shock trains at 10 Hz, every 3 sec; averaged (*AVG*), augmenting cortical responses are depicted in *inset*] produced an increased frequency of the cortical rhythm; this effect outlasted thalamic stimulation as a self-sustained oscillation at 1.6 Hz. *Top* and *bottom traces* are continuous recordings.

mic spike bursts building up the delta oscillation of thalamocortical cells. Since thalamocortical cells do not generally possess recurrent axonal collaterals (see Steriade et al., 1990b), local-circuit cells are not directly driven by thalamic relay cells located in the same nucleus. However, this morphological feature is possible when intranuclear recurrent axonal collaterals of cortically projecting thalamic cells are demonstrated. Of all thalamic nucleus so far investigated, this is seemingly the case of only dLG nucleus (Friedländer et al., 1981; Humphrey and Weller, 1988). In this case, however, no systematic electron microscopic studies have been performed and one may ask whether the collaterals were given off earlier in their route to the perigeniculate sector of the RE nucleus.

Nonetheless, electrophysiological evidence of delta synchrony in the dLG nucleus was recently provided in two intracellular studies, *in vitro* (Soltesz and Crunelli, 1992) and *in vivo* (Nuñez et al., 1992b). These experiments showed that, in addition to the intrinsically oscillating cells, other dLG neurons displayed the same delta frequency, but their rhythm was synaptically generated through coupling of thalamic relay cells by intranuclear axonal collaterals. Indeed, the rhythmic depolarizations of the synaptically induced delta rhythm consisted of grouped EPSPs and FPPs, developing into clocklike LTSs under slight hyperpolarization (Nuñez et al., 1992b). In the *in vitro* condition, the low-frequency, rhythmic EPSPs were abolished by TTX (Soltesz and Crunelli, 1992).

Thus, both long- and short-range circuits, possibly inhibitory as well as excitatory, can synchronize thalamic neurons. Synchronization within the frequency range of delta rhythm has recently been detected by multisite recordings in the RE and various dorsal thalamic nuclei of anesthetized or naturally sleeping animals (D. Contreras and M. Steriade, unpublished observations). However, the epochs during which synchronization was evident were rather limited in time. This probably explains why clocklike delta potentials, as illustrated in the present Figures 1 and 2, were seen in only a minority (17%) of cortical neurons. Also, the visible association at the cortical level between the slow and delta rhythms depends, on one hand, on the synchrony of thalamic neuronal pools exhibiting delta oscillation, and, on the other hand, on the recording sites in the cortical target areas. Future experiments, with multiple fine and coarse electrodes inserted in thalamic nuclei and related neocortical areas (as determined by ortho- and antidromic identification procedures), should quantitatively assess the association of slow and delta rhythms at single-cell and population levels in various thalamocortical systems and to determine the state dependency of this combined rhythmicity (e.g., its possible occurrence during late stages of natural sleep, as opposed to the presumed association between the slow rhythm and spindle oscillations in early sleep stages).

(2) Second, the thalamically generated delta oscillation is reflected on the EEG after intercalated excitatory and inhibitory processes in complex cortical networks. This passage probably accounts for the smoother, less regular aspect of EEG waves within delta frequencies. Thalamically generated events are transformed by multiple synaptic operations within the cortex, probably in a more complex way than that by which the signals of cortical origin undergo changes in the thalamus before being processed back to the cortex. For example, the single action potentials occurring within the delta frequency during the interdepolarization lulls of the slow rhythm are cyclically interrupted in some neurons (Fig. 1), probably because the slow cortical rhythm is imposed upon thalamic cells as a rhythmic depolarizing event (see Figs. 9, 10 in Steriade et al., 1993b) and this depolarization would bring thalamic relay cells out of the voltage range where delta rhythm is generated. As to the thalamic rhythms transmitted to cortex, the grouping of delta potentials within the frequency of slow oscillation (Fig. 3) is attributable to the rhythmic interruption of delta events by prolonged GABAergic synaptic processes and/or Ca^{2+}-dependent

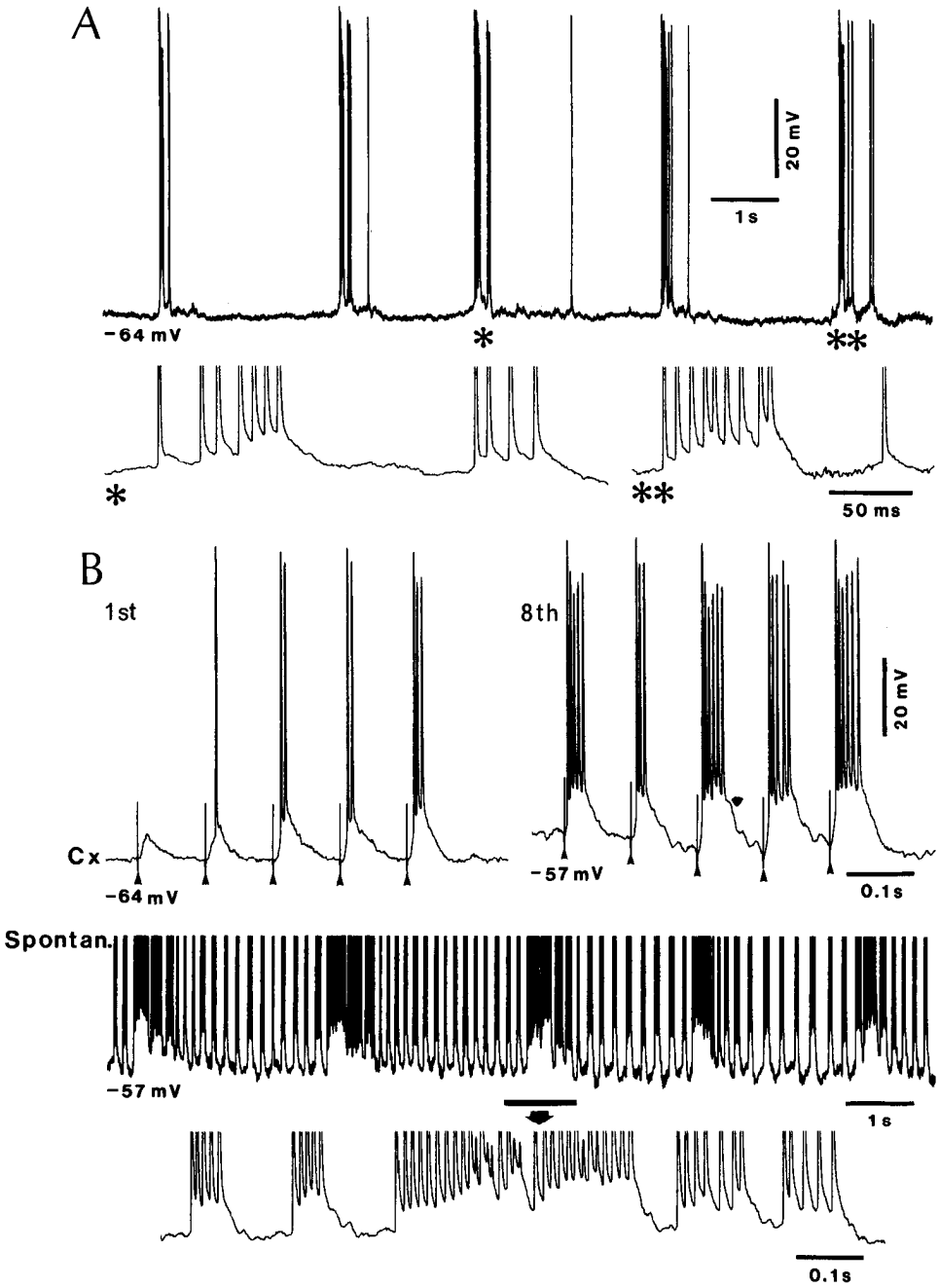

Figure 14. Self-sustained oscillation after repetitive cortical stimulation in a thalamically lesioned animal: intrinsically bursting neuron, recorded at 1.5 mm in area 7. *A*, Slow rhythm (0.4 Hz). Bursts marked by *one* and *two asterisks* are expanded below (spikes truncated). *B*, Responses of the same cell to repetitive stimulation (five-shock trains at 10 Hz, repeated every 3 sec) of the contralateral area 7. The augmenting responses to the first and eighth trains are illustrated. Spontaneous (*Spontan.*) activity is illustrated after 15 such cortical shock trains.

K^+ currents in cortical neurons (see evidence for this in Steriade et al., 1993a).

(3) Last, although we know that stereotyped delta oscillations are generated in the thalamus, we still need conclusive evidence of whether or not delta waves may also originate in the cortex, in the absence of the thalamus. If so, this would also explain the irregularity and polymorphism of EEG delta waves. Earlier experiments indicated that large thalamic lesions suppressed cortical spindles, but EEG delta waves were preserved in the cortex (Villablanca and Salinas-Zeballos, 1972). This was a major argument for the cortical origin of EEG delta rhythm. Total thalamectomy is, however, a heroic procedure that may leave intact some parts of the thalamus. Indeed, the anatomical study of those "athalamic" animals showed that "the thalamus was *almost* completely removed" (Villablanca and Salinas-Zeballos, 1972, p 386). Morphological work during the past 15 years demonstrated that some thalamic nuclei, to only mention the VM and intralaminar CL-PC wing, have diffuse projections to the neocortical convexity (see reviews in Jones, 1985; Macchi and Bentivoglio, 1986). This might explain, in the version of the thalamic genesis of delta oscillation, the presence of EEG delta waves on some cortical fields. Accepting, however, the results of experiments with extensive thalamic lesions, leaving intact delta waves in the cortex, we have to take into serious consideration the possibility that at least some types of delta waves arise in the cortex after total thalamic destruction. Although this issue is not settled at the present time, we would like to suggest that the clocklike, stereotyped delta oscillation,

occurring during the interdepolarization lulls (Fig. 1), is generated by intrinsic properties of thalamic cells, whereas the cellular events within the delta frequency and superimposed upon the slow depolarizing envelopes (Fig. 3) may have a more complex origin, including their genesis within the cerebral cortex.

The slow cortical rhythm modulates the slow rhythm of thalamically generated spindle sequences

Spindles (7–14 Hz) are generated in the thalamus in the absence of the cerebral cortex (Morison and Bassett, 1945), but cortical volleys may reinforce this type of thalamic rhythmicity, "presumably by facilitation fed back" (Morison and Dempsey, 1943, p 307). This considerably important statement was generally neglected, in spite of similar ideas on reverberating thalamocorticothalamic circuits (Dusser de Barenne and McCulloch, 1938; Chang, 1950).

The pacemaking role of the RE thalamic nucleus in spindle genesis was demonstrated by absence of spindles in thalamic territories disconnected by lesions or naturally devoid of inputs from the RE nucleus (Steriade et al., 1985; Paré et al., 1987) and by preservation of spindle rhythmicity in the isolated RE nucleus, that is, deafferented from the dorsal thalamus and cerebral cortex (Steriade et al., 1987). These results from cat experiments are strengthened by abolition of spindling in thalamocortical systems after RE lesions in rats (Buzsáki et al., 1988). Recently, the role of RE neurons in promoting and synchronizing EEG spindles was confirmed by elicitation of spindling after chemical excitation of RE perikarya; the phenomenon was so impressive that spindle sequences protruded into the state of rapid eye movement sleep, when the EEG is usually desynchronized (Marini et al., 1992).

Spindle waves are grouped in sequences lasting for 1.5–3 sec and recurring periodically, every 5–10 sec. Although, with the benefit of hindsight, this slow (0.1–0.2 Hz) rhythm can be seen in early EEG recordings of animals and humans, it was only lately described (Steriade and Deschênes, 1984). As yet, we have no explanation about the intrinsic or synaptic origin of the slow rhythm separating the sequences of spindle waves (interspindle rhythm). Studies of cat dLG slices done by Crunelli's group (Leresche et al., 1991) have reported that sequences of "spindle-like" waves (so termed by those authors) recurred every ≈10 sec, even after TTX application, thus pointing to the intrinsic nature of this slow (0.1 Hz) rhythm. However, the frequency of those "spindles" was ≈2–2.5 Hz (at least three times lower than the frequency of bona fide spindles in a living animal) and the mean duration of a "spindle" sequence was 8.5 sec (three to four times longer than *in vivo*). To add to these dissimilarities, DC depolarization decreased the frequency of "spindles" and resulted into their transformation into the pacemaker oscillation of the delta type (Leresche et al., 1991), whereas *in vivo* experiments showed that the transformation of spindles into delta oscillation is brought about by hyperpolarization of thalamic cells with either DC current (Steriade et al., 1991; Nuñez et al., 1992a) or application of NMDA blockers (Buzsáki, 1991). Lastly, the so-called "spindles" in that *in vitro* study were depolarizing events, whereas all *in vivo* intracellular studies of thalamocortical neurons have described this oscillation as consisting of rhythmic (7–14 Hz) hyperpolarizing IPSPs, associated with a large increase in membrane conductance (Andersen and Sears, 1964; Maekawa and Purpura, 1967; Deschênes et al., 1984). These comparisons indicate that the conclusions about spindles based on those *in vitro* data are at least questionable, especially when no sign of interneuronal cooperation is detected. While some cellular types oscillate by virtue of their intrinsic currents (see above, Interaction between slow and delta waves; and below, The role of intrinsically bursting cells in cortical oscillations), their rhythms should be synchronized to be reflected as EEG macropotentials.

All experimental evidence reviewed above showed that spindling is a typical network operation, driven and synchronized by the RE thalamic nucleus. Some intrinsic properties of RE and thalamic relay cells may, however, be decisive in shaping the pattern of spindles. For example, this may be the case for the termination of spindle sequences. McCormick (1992) has suggested that changes in I_h activation curve and kinetics, ascribed to an increase in intracellular Ca^{2+} concentration after Ca^{2+}-dependent LTSs (Hagiwara and Irisawa, 1989), may account for the depolarization terminating a spindle sequence. Other scenarios accounting for the same phenomenon include the desynchronization of RE synaptic network toward the end of a spindle sequence and/or the fact that spindle-related RE-cell rhythmic bursts end with a tonic tail (Domich et al., 1986; Steriade et al., 1986). Both these possibilities may contribute to a diminished efficacy of RE neurons in producing sharp IPSPs in target thalamocortical neurons. Still other factors accounting for the slow rhythm of thalamic spindle sequences might be similar or even slower oscillations of locus coeruleus (Akaike, 1982), rostral midbrain reticular (Oakson and Steriade, 1982), and mesopontine cholinergic (Steriade et al., 1990a) neurons.

Is the slow (0.1–0.2 Hz) interspindle thalamic rhythm *entirely* due to a similar rhythm (≈0.3 Hz) in corticothalamic neurons, as described in this series of articles? That this is not the case, although the cortical rhythm potently modulates the thalamic one, is indicated by a series of results.

(1) Both rhythms of spindle waves (7–14 Hz) and interspindle sequences (0.1–0.2 Hz) exist in the thalamus after bilateral decortication and high brainstem transection (Morison and Bassett, 1945). Also, the isolated RE thalamic nucleus, disconnected from dorsal thalamic as well as cortical inputs, still displays spindles as well as their rhythmic recurrence with a slow rhythm (Steriade et al., 1987).

(2) Conversely, after extensive thalamic lesions, resulting in complete disappearance of cortical EEG spindles, the slow rhythm of cortical neurons survived (see Figs. 10, 12).

(3) Intracellular recordings of cortical pyramidal tract neurons showed a close relationship between oscillations in membrane potential at 7–14 Hz and spontaneous or thalamically induced spindle waves recorded at the cortical surface (Jasper and Stefanis, 1965; Creutzfeldt et al., 1966). By contrast to the close time-relation between spindle oscillations in cortical cells and the same rhythm in cortical EEG, both dependent upon the thalamus, the depolarizing envelopes of the slow cortical rhythm consisted of EPSPs and IPSPs that sometimes appeared at 7–14 Hz, but were more commonly seen at lower (3–4 Hz) or higher (15–30 Hz) frequencies. Thus, the components of the slow cortical oscillation are different from those of the slow spindle rhythmicity. Pure spindling was only obtained under barbiturate anesthesia (Fig. 7).

(4) The final arguments pointing to the different sites of genesis and mechanisms of the slow cortical oscillation and the slow rhythm of spindle oscillation arise from the patterns of associated EEG wave complexes recurring at 0.1–0.3 Hz. The EEG

complex consisted of a positive–negative or negative–positive deflection at the surface, which was simultaneous with the onset of the depolarization and action potentials in the slow cellular rhythm, followed after ≈0.4 sec by a sequence of spindles at ≈10 Hz (Figs. 1*A*, 2*D*). This suggests that the slow rhythm of cortical neurons drives RE cells and, subsequently, dorsal thalamic neurons to trigger spindles in thalamocortical systems. This possibility is substantiated by data reported in the final article of this series (Steriade et al., 1993b). Besides, the slow cortical rhythm may appear in advance of full development of cortical spindles that can be seen later on, with increasing EEG synchrony (see Figs. 1*A*, 5). By no means would this aspect imply that, in the chronological order of sleep stages, the slow cortical rhythm is more precocious than spindling. It only indicates that the thalamic neuronal pools have to be synchronized before spindles are visible over the cortex, and this process of synchronization goes in parallel with that of oscillations generated by the cerebral cortex. In support of this assumption, a previous article showed that spindles are generated in the thalamus from the first postnatal day, but they are fully transferred to the cortex only by the eighth or ninth day (Domich et al., 1987), only with increased synchrony due to continuing synaptogenesis after birth.

To sum up, both the thalamus and cortex are endowed with mechanisms required to generate a slow oscillation. The mechanism(s) of thalamic slow interspindle rhythm still remains a mystery and should be investigated. Besides the long-term synaptic and/or intrinsic properties that should be investigated to this end, the possibility exists that the slow interspindle rhythmicity of cortically disconnected thalamic cells results from their special metabolic properties that could periodically interrupt their phases of activity by long-lasting lulls (see Pape, 1992). In natural conditions, when the thalamus and cerebral cortex interact through reciprocal projections, the slow rhythms of their neurons are synchronized and mutually reinforced.

The role of intrinsically bursting cells in cortical oscillations

Intrinsically bursting cortical cells have been initially described by Connors et al. (1982) and McCormick et al. (1985) in slices from sensorimotor cortex of rodents. Some of these neurons display rhythmic bursts in response to single volleys applied to the cortical slice or direct cellular stimulation (Agmon and Connors, 1989; Chagnac-Amitai and Connors, 1989b; Silva et al., 1991). Similar repetitive spike bursts, up to a frequency of 10 Hz, have been elicited by depolarizing current pulses in our *in vivo* study of cat association cortical neurons (see Fig. 4 in Nuñez et al., 1993). However, synaptic volleys from the thalamus are less efficient in driving intrinsically bursting cortical cells at high rates, as seen from their lower-frequency (2–6 Hz) bursts during EEG spindles at 10–13 Hz (Figs. 6, 7). In the experimental condition of completely or partially suppressed inhibition, the frequency of spike bursts may be higher (Chagnac-Amitai and Connors, 1989a,b).

The discharge patterns of intrinsic bursts in the present study on cat are very similar to those described in cortical slices of rodents. In our experiments, intraburst frequencies of action potentials were ≈150–250 Hz, the fully developed burst often followed the occurrence of one or two single spikes, and repetitive stimuli dramatically enhanced the number and frequency of bursting action potentials (see Fig. 14), much the same as reported in rat neocortical slices (see Fig. 10 in Chagnac-Amitai and Connors, 1989b). The intracellularly stained bursting neurons in this study were pyramidal elements (see Fig. 10 in Steriade et al., 1993a), as also documented in rat sensorimotor slices (McCormick et al., 1985). While the intrinsically bursting cells of rat seem to be confined to layer V in both somatosensory and visual cortices (Chagnac-Amitai et al., 1990; Mason and Larkman, 1990), we also found such a cell in layer III of association area 5, but our sample of stained bursting cells is to small to draw definite conclusions.

Bursting neurons probably have a great impact on adjacent as well as distant, synaptically coupled, neurons. All intrinsically bursting cells investigated in our study were oscillating within the slow rhythm. They were strongly and consistently excited during the slow depolarizing envelopes described here (see Figs. 6, 14). The possibility exists that intrinsically bursting cells receive their inputs from each other, as suggested by Chagnac-Amitai and Connors (1989b) from data indicating that regular-spiking cells are only briefly excited during synchronous activity (see also Thomson et al., 1988). This is consistent with data illustrated in Figure 3*B* in which the slow oscillations of a bursting cell were closely time related with focal waves recorded through the same micropipette, reflecting summated PSPs in a pool of neurons, possibly of the same type. That intrinsically bursting cells may indeed form an interconnected network is suggested by our data showing self-sustained oscillation in such a neuron after prolonged stimulation of the homotopic area in the contralateral cortex (Fig. 14). In that recording, the thalamus was extensively lesioned and, thus, the prolonged oscillation with an almost paroxysmal pattern is attributable to intrinsic cortical circuits. Even more powerful synchronization is expected in a brain-intact preparation when spike bursts are transferred to thalamocortical cells, with obvious consequences for the spread of synchronous activity. Repetitive cortical volleys are indeed able to produce resonance phenomena in thalamic cells, with spontaneous spike bursts persisting with similar or identical intra- and interburst frequencies if compared to those elicited in the final stage of stimulation (see Fig. 7 in Steriade, 1991). In both amygdalo-hippocampal circuits (Steriade, 1964) and corticothalamic systems (Steriade et al., 1976), self-sustained activities, like those outlasting the stimulation period in Figure 14, may lead to paroxysmal events of the absence petit mal type or other forms of epilepsy. The role of thalamic neurons in the synchronization of the cortically generated slow oscillation is further documented in the next article.

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