[Frontiers in Bioscience 8, d878-899, May 1, 2003]

THE CORTICOTHALAMIC SYSTEM IN SLEEP

Mircea Steriade

Laboratory of Neurophysiology, Faculty of Medicine, Laval University, Quebec, Canada G1K 7P4

TABLE OF CONTENTS

1. ABSTRACT

The transition from wakefulness to NREM sleep is associated with typical signs of brain electrical activity, characterized by prolonged periods of hyperpolarization and increased membrane conductance in thalamocortical (TC) neurons, with the consequence that incoming messages are inhibited and the cerebral cortex is deprived of signals from the outside world. There are three major oscillations during NREM sleep. Spindles are generated within the thalamus, due to thalamic reticular (RE) neurons that impose rhythmic inhibitory sequences onto TC neurons, but the widespread synchronization of this rhythm is governed by corticothalamic projections. There are two types of delta activity: clock-like waves generated in TC neurons by the interplay between two hyperpolarization-activated inward currents; and cortical waves that survive extensive thalamectomy. The hallmark of NREM sleep activity is the slow oscillation, generated intracortically, which has the virtue of grouping the other types of sleep activities, thus leading to a coalescence of different rhythms that can only be observed in intact-brain animals and humans. Far from being epiphenomena, with no functional role, NREM sleep oscillations, particularly spindles and their experimental model augmenting responses, produce synaptic plasticity in target cortical neurons and resonant activity in corticothalamic loops, as in "memory" processes. Upon brain arousal, spindles are blocked by inhibition of RE neurons, the spindles' pacemakers; clock-like delta rhythm is obliterated by depolarization of TC neurons; and the cortically generated slow oscillation is abolished by selective erasure of its hyperpolarizing components. Fast (beta and gamma) oscillations are roduced by the depolarizing effects of mesopontine cholinergic neurons acting on TC neurons and nucleus basalis neurons acting on cortical neurons.

2. NEURONAL SUBSTRATES OF BRAIN DISCONNECTION DURING NREM SLEEP

The mechanisms underlying the onset of sleep are mainly explored at the neuronal level. However, one should consider that the genesis and maintenance of the enduring state of sleep are hardly attributable to only conventional neuronal mechanisms, which operate on relatively short time scales. It is then conceivable that the commendable efforts made by recording single neurons in order to understand how one falls asleep will only make sense when concerted studies on sleep humoral factors and on their modulatory actions upon neurons in critical brain areas will fully disclose the mechanisms of falling asleep. At this time, we know little about the effects of sleep-promoting chemical substances (1, 2) upon formally identified neurons with hypothesized hypnogenic properties.

The defining signs of the period when one falls asleep are peculiar changes in brain electrical activity, which are the cause, rather than the reflection, of a quiescent behavioral condition. Indeed, the oscillations of the electroencephalogram (EEG) that define the transition from wakefulness to NREM sleep, mainly spindles, are associated with long periods of hyperpolarization and increased membrane conductance in thalamocortical (TC) neurons, with the consequence that afferent messages are blocked and the cerebral cortex is deprived of external signals (3). Following the appearance of these initial signs, other oscillatory types mark the late stage of NREM sleep and they further deepen the inhibition of thalamic and cortical cells.

Although thalamic responsiveness is globally decreased throughout NREM sleep, due to the hyperpolarization of TC neurons, gating of afferent signals is most effective during epochs in which spindles are present because this oscillation is built-up by prolonged IPSPs in thalamic relay neurons. The first, declining phase of the hyperpolarization in each spindle wave is most effective in reducing the amplitude and duration of incoming messages (4). These data, from experimental animals, are corroborated in humans by investigating the role of spindles in gating information processing to protect

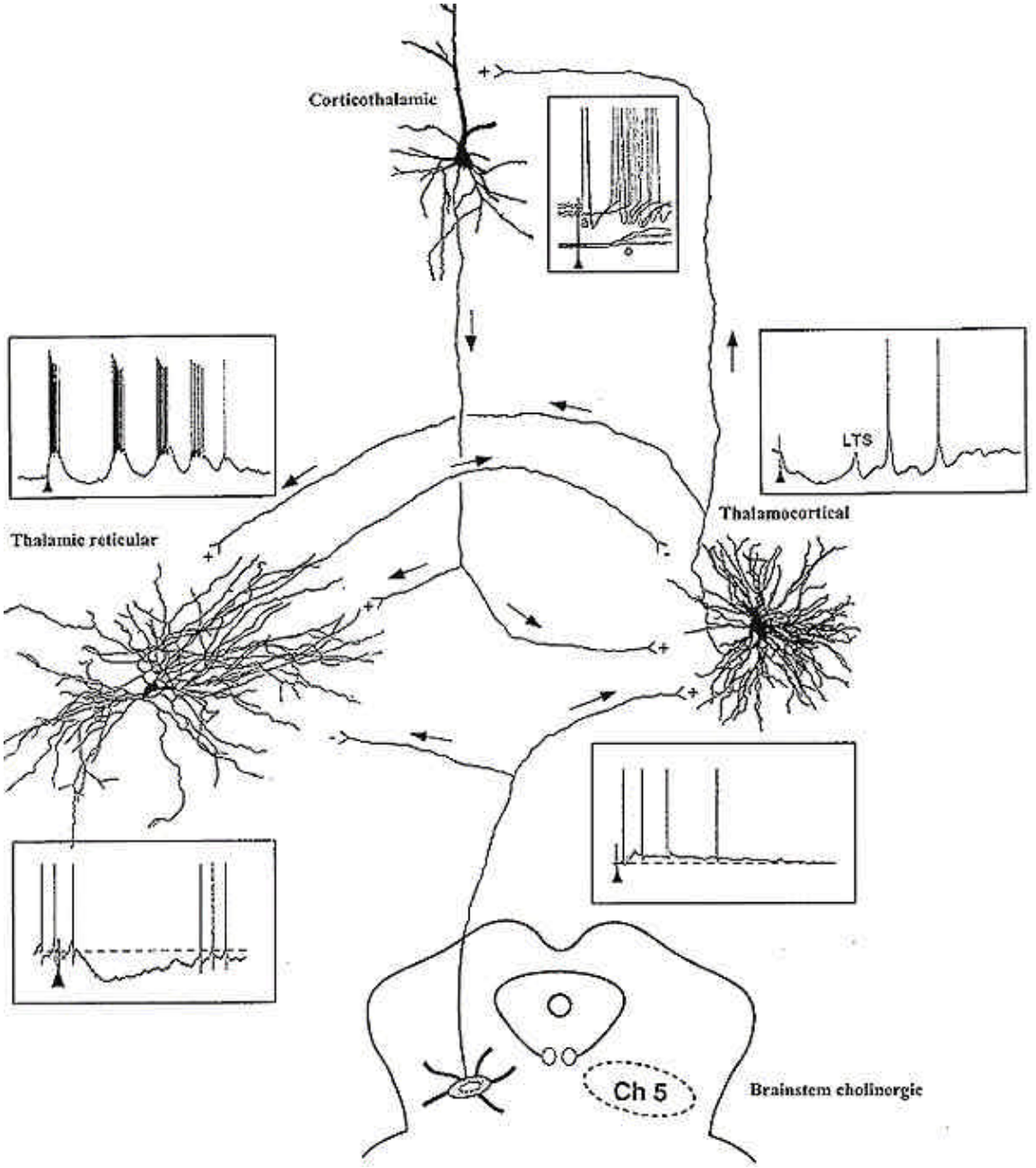

Figure 1. Neuronal loops in corticothalamic networks implicated in coherent oscillations and their control by brainstem cholinergic neurons. The top three neurons have been recorded and stained intracellularly in anesthetized cats. The direction of their axons is indicated by arrows. Insets represent their responses to thalamic and cortical stimulation (arrowheads point to stimulus artifacts). The corticothalamic neuron (spikes truncated) from area 7 responded to thalamic stimulation of centrolateral intralaminar nucleus with antidromic (a) and orthodromic (o) action potentials (top superimposition, at a membrane potential of -55 mV). At more hyperpolarized levels (bottom superimposition, at -64 mV), the antidromic response failed but the orthodromic response survived as subthreshold EPSPs. In addition to such closed loops, in which the cortical neuron is excited from a given thalamic nucleus and projects back to the same nucleus, cortical neurons may project to thalamic nuclei that are different from those representing the input source for the cortex. Such cases provide the substrate for distribution of activities beyond the site of their generation in the cerebral cortex. The thalamic reticular GABAergic neuron responded to cortical stimulation with a high-frequency spike-burst, followed by a sequence of spindle waves on a depolarizing envelope. The thalamocortical (TC) neuron responded to cortex stimulation with a biphasic IPSP, leading to a low-threshold spike (LTS) and a sequence of hyperpolarizing spindle waves. For the sake of simplicity, local-circuit inhibitory neurons in cortex and thalamus are not illustrated. Shown below, the dual effects of brainstem cholinergic neurons, namely hyperpolarization of the thalamic reticular neuron and depolarization of the thalamocortical neuron. Modified from Steriade (20).

the sleeper from disturbing sounds (5). Thus, besides the steady hyperpolarization of TC neurons during NREM sleep (6), spindles represent an additional, significant factor to prevent information to reach the cortex during this sleep state.

Since the thalamus is the first relay station where inhibition of synaptic transmission is observed from the very onset of sleep, as determined by the fact that incoming volleys (monitored by presynaptic components of responses) are not altered in relay stations before the thalamus (7), the neuronal substrates of brain disconnection during NREM sleep should be searched in the two major cell-classes of the thalamus: TC glutamatergic neurons and thalamic reticular (RE) GABAergic neurons. Local-circuit inhibitory neurons are absent in most thalamic nuclei of rodents and play an ancillary role in the generation of NREM oscillations in felines and primates (8, 9, 10). The basic circuitry involving TC and RE neurons, and their relations with deeply lying neocortical neurons and with activating cholinergic neurons located in the mesopontine reticular core, are depicted in Figure 1.

Although all corticothalamic axons are glutamatergic (thus exerting excitatory actions on both RE and TC neurons), the effect of artificial or natural cortical volleys is opposite on each of these two thalamic neuronal types. Electrical stimuli or natural synchronous cortical volleys (which occur during NREM sleep when neurons exhibit highly coherent activity) produce excitation and rhythmic spike-bursts over a depolarizing envelope in RE neurons, whereas TC neurons simultaneously display rhythmic and prolonged inhibitory postsynaptic potentials (IPSPs), occasionally followed by rebound excitations (Figure 1). Thus, the bisynaptic inhibition of TC neurons, induced by cortex through a prior synaptic relay in GABAergic RE neurons, overcomes the direct excitation of TC neurons. This is substantiated by recent results showing that the numbers of glutamate receptor subunits GluR4 are 3.7 times higher at corticothalamic synapses in RE neurons, compared to TC neurons, and that the mean peak amplitude of corticothalamic excitatory postsynaptic currents (EPSCs) is about 2.5 higher in RE, than in TC, neurons (11). The differential effects exerted by synchronous firing of corticofugal neurons on RE and TC neurons are important because a series of natural phenomena, occurring especially in the sleeping brain, depend on varying functional states of RE neurons, which have different consequences on TC neurons. The most potent effects are exerted by RE neurons when they fire prolonged, rhythmic, high-frequency spike-bursts, which are the signature of these GABAergic neurons from the very onset of NREM sleep, whereas the same inhibitory thalamic neurons discharge tonically, in the single-spike mode during waking and REM sleep (12). During NREM sleep, and even more so during some types of electrical seizures that develop from sleep patterns, the spike-bursts fired by RE neurons induce greater postsynaptic inhibitory responses in TC neurons than those elicited by single spikes. Such potent IPSPs, associated with increased membrane conductance, account for the disconnection of TC networks from the outside world during NREM sleep and for unconsciousness during spike-wave seizures (13), as in absence epilepsy that preferentially develops during NREM sleep (14).

The synchronous activity of corticothalamic neurons, which characterizes NREM sleep, is effective in setting into action the thalamic neuronal equipment to reinforce thalamically generated spindles. Moreover, as shown in the next section, the cortically generated slow oscillation, a hallmark of NREM sleep in animals and humans, has the virtue of grouping other NREM sleep rhythms generated in the thalamus, such as spindles and clock-like delta waves. This accounts for the coalescence of all NREM sleep oscillations (15) and reinforces the concept (16, 17) that, in brains with intact connectivity, there are no simple rhythms, as is the case in extremely simplified preparations (such as brain slices) in which one can see, at best, spindles or slow oscillation in isolation.

By contrast, brainstem core systems, among them cholinergic ones, obliterate NREM oscillations and promote patterns that characterize brain-activated states of waking and REM sleep. This is due, on one hand, to the inhibitory action (hyperpolarization with increased membrane conductance) exerted by brainstem cholinergic neurons on thalamic RE GABAergic neurons (Figure 1) (18) that are pacemakers of spindle oscillations (see below, *Spindles …*). On the other hand, the same mesopontine cholinergic neurons exert prolonged depolarizing (muscarinic-mediated) actions on TC neurons (Figure 1) (19), thus bringing them to membrane potential levels at which low-threshold spike-bursts during spindles are prevented, and they also block the hyperpolarization-activated thalamic delta waves (21; see below, Figure 12).

The complex circuits of intrathalamic, corticothalamic and brainstem-thalamic networks require investigations in intact-brain animals. For details on properties of different neuronal types in these circuits and on their alterations with shifts in states of vigilance from NREM sleep to either waking or REM sleep, the reader is referred to recent reviews and monographs (14, 16, 17).

3. THREE TYPES OF BRAIN RHYTHMS DURING NREM SLEEP: THE UNIFIED CORTICOTHALAMIC SYSTEM

The mechanisms of generation and synchronization of the three major oscillatory types that characterize NREM sleep are described in what follows.

3.1. Spindles, a thalamic rhythm under neocortical influence

This sleep rhythm (7 to 14 Hz in cats, 12 to 15 Hz in humans) consists of sequences that recur rhythmically, every 2 to 5 s (Figure 2*B*). Since the old days of clinical EEG (22), it was observed that “low-frequency” and “fast-frequency” spindles (~12 Hz and ~14 Hz, respectively) show a different topographic localization, with the former localized more anteriorly. A more unified way to see different spindles’ frequencies is based on

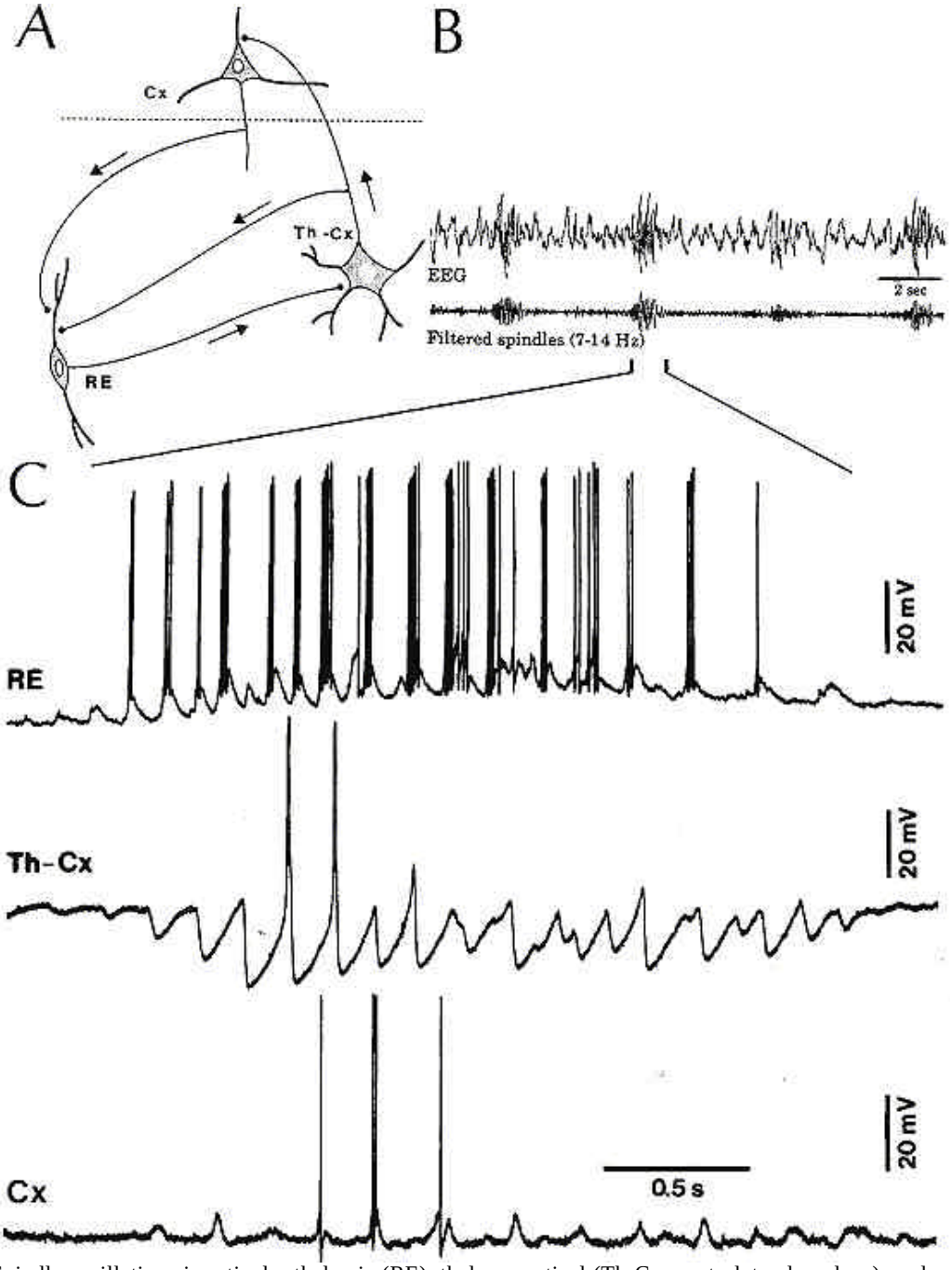

Figure 2. Spindle oscillations in reticular thalamic (RE), thalamocortical (Th-Cx, ventrolateral nucleus), and cortical (Cx, motor area) neurons. *A*, circuit of three neuronal types. *B*, two rhythms (7-14 Hz and 0.1-0.2 Hz) of spindle oscillations in cortical EEG. *C*, intracellular recordings in cats under barbiturate anesthesia. Note rhythmic spike-bursts of RE neuron during a spindle sequence and concomitant IPSPs leading to post-inhibitory rebound bursts in Th-Cx neuron. See also text. Modified from Steriade and Deschênes (45).

results using intracellular recordings of TC neurons: low-frequency spindles are due to long-lasting hyperpolarizations (lasting 100-150 ms) followed by rebound spike-bursts, whereas relatively shorter hyperpolarization-rebound sequences (70-100 ms) account for faster spindles. The possibility is open that TC neurons projecting to anterior cortical fields in humans display longer hyperpolarizations during spindles, thus accounting for lower-frequency of spindles.

In essence, spindles arise in GABAergic thalamic RE neurons whose rhythmic spike-bursts induce IPSPs in target TC neurons; these IPSPs de-inactivate a transient low-threshold Ca^{2+} current that promotes burst firing,

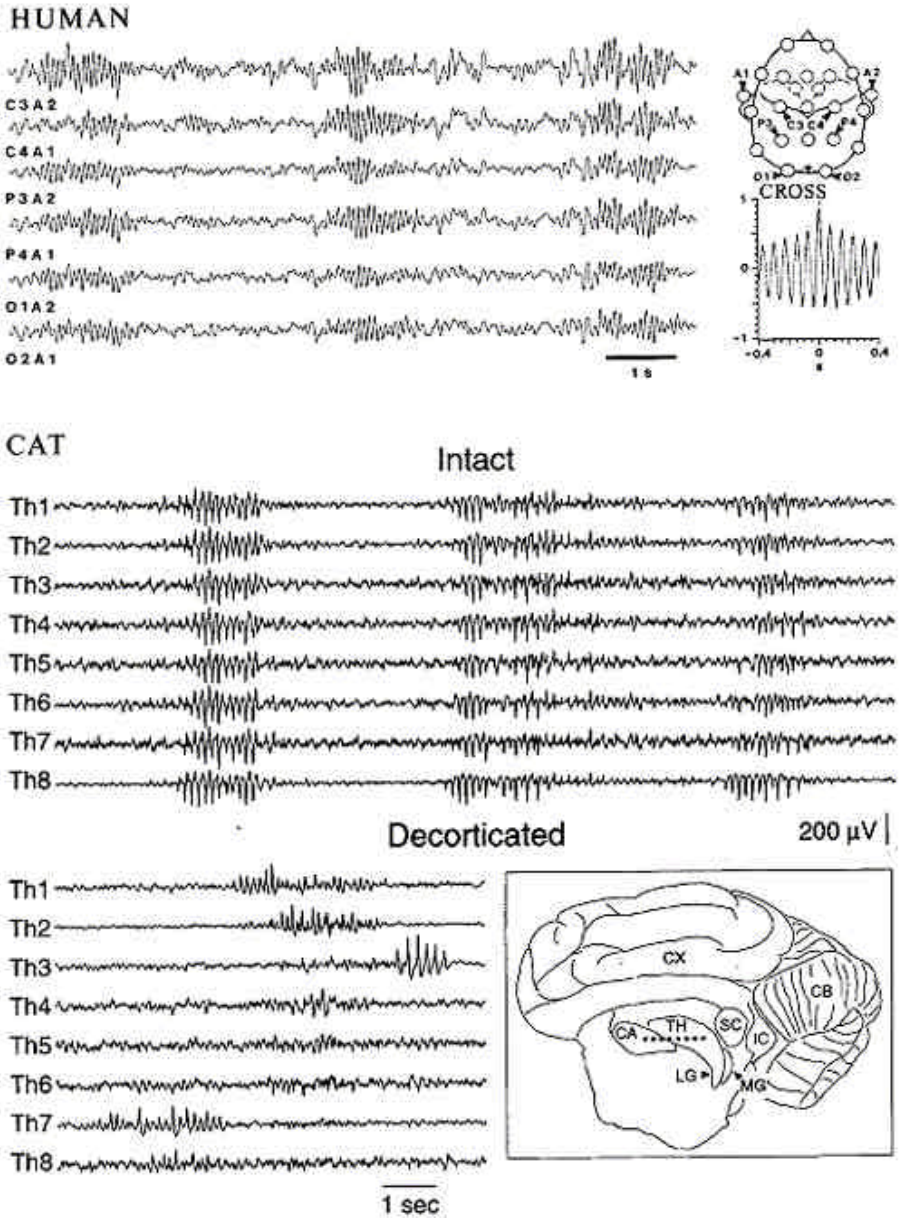

Figure 3. Cortical spindle sequences occur nearly simultaneously during natural sleep of humans and cats, but decortication disorganizes the widespread coherence of thalamic spindles. In the *top panel* illustrating natural sleep in *HUMAN*, spindles were recorded from six standard EEG derivations (indicated in the schematic at right, arrowheads) in a normal subject, during sleep stage 2. Cross-correlations of individual spindle sequences (n = 15) were calculated between C3A2 and each one of the other channels. Averaged correlations (*CROSS*) showed rhythmicity at 14 Hz and central peak values between 0.7 and 0.9. Below, spindles were simultaneously recorded from 7 leads in the thalamus of intact-cortex cat under barbiturate anesthesia. Note the virtual simultaneity of spindle sequences. After decortication (see scheme), recordings from virtually same thalamic sites showed disorganization of spindle simultaneity. Modified from Contreas *et al.* (33, 34).

which is transferred to cortical neurons where it induces rhythmic EPSPs and occasional action potentials (Figure 2*C*). That GABAergic thalamic RE neurons are pacemakers of spindles was demonstrated since the 1980s: spindles disappear in TC systems after disconnection from RE neurons (23) and they are preserved within the RE nucleus disconnected from the remaining thalamus and cerebral cortex (24). These experimental data were corroborated in different types of computational models of isolated RE neurons, which displayed oscillations within the frequency range of spindles (25, 26, 27).

The failure to detect spindles in the visual sector of the RE nuclear complex investigated in slices maintained *in vitro* (28) was attributed (29) to an incomplete collection of intact RE neurons due to the slice procedure that cuts the very long dendrites of RE neurons, which are essential for the generation of spindles (30, 31). Also, thalamic slices

lack inputs from brainstem monoaminergic systems that depolarize RE neurons, thus allowing the expression of spindles (32).

Another significant difference between spindles recorded *in vivo* or *in vitro* is the nearly simultaneous appearance of spindle sequences during natural NREM sleep in the intact brains of animals and humans (Figure 3) (33, 34), as opposed to the systematic propagation of spindles in slices from the visual thalamus (35), the only thalamic sector in which spindle-like waves could be recorded *in vitro.* We hypothesized that the absence of neocortex in thalamic slices accounts for this difference and demonstrated that, following decortication, spindle sequences are no longer simultaneous in the thalamus (Figure 3) without however displaying propagation as in slices. These data emphasize the importance of neocortex in synchronizing an oscillation generated in the thalamus. It is also known that cortical volleys act as the most powerful trigger for spindle induction in the thalamus. To avoid antidromic activation of TC-cells' axons and axon-reflex excitation of pacemaking RE neurons, thalamic spindles can also be elicited from the contralateral cortex (36). This involves the callosal and corticothalamic pathways (37, 38). The synchronous firing of cortical neurons during the slow oscillation in NREM sleep sets into action the thalamic neuronal equipment and, thus, a brief sequence of spindles is seen after each cycle of the slow oscillation (see below, Figure 5; 39, 40, 41). All these data demonstrate that, though sleep spindles are generated within the thalamus, they are under the synchronizing control of the neocortex.

In addition to their role in the widespread synchronization and near-simultaneity of spindle sequences, corticothalamic neurons are operational in the process of terminating individual spindle sequences. This is due to the depolarizing actions of corticothalamic neurons that lead to different duration of spindle-related IPSPs in TC neurons, with the consequence of different times at which postinhibitory rebound spike-bursts are fired, so that the synchrony in the whole thalamic circuit is disrupted and spindles are terminated. The most important source of spindle desynchronization is thought to be the corticothalamic input because, during the late phase of spindles, neocortical neurons become tonically depolarized, eventually leading to firing, and spike-triggered-averages by cortical neurons do not reveal a phase relationship between cortical and TC neurons (42). Another, intrinsic-cell factor accounting for the termination of spindles may be the Ca^{2+}-induced up-regulation of the hyperpolarization-activated depolarizing (cation) current (I_H) (43, 44). To test the contribution of network (corticothalamic) or intrinsic (I_H) factors in terminating spindle sequences, a computational study investigated a model with four layers of thalamic and cortical neurons. The RE-TC isolated network oscillated infinitely and up-regulation of I_H alone was *not* sufficiently strong to terminate spindling. With the addition of the corticothalamic feedback, the spindles in the RE-TC network were short, resembling that observed after a highly synchronous cortical volley during NREM sleep slow oscillation (42).

To sum up, *(a)* the first part of a spindle sequence is generated in the pacemaker RE nucleus; *(b)* during the first 2-to-4 IPSPs composing the spindles, TC neurons do not display rebound spike-bursts (see Figure 2), thus they do not return signals to RE neurons and do not contribute to this phase of a spindle sequence; *(c)* the middle part of a spindle sequence is due to the activity in the RE-TC-RE loop; and *(d)* the termination of spindles is due to the depolarizing action of I_H and/or the depolarizing action of corticothalamic neurons.

3.2. Delta waves: two different (thalamic and cortical) components

With deepening of NREM sleep, delta waves (1-4 Hz) appear and prevail over spindles. There are two types of delta waves that are distinct as to their site of origin and underlying cellular mechanisms. *(a)* The thalamic component of delta waves has a clock-like pattern and depends on two inward currents of TC neurons: a hyperpolarization-activated current, I_H, carried by Na^+ and K^+, which is expressed as a depolarizing sag of membrane potential toward rest; and a transient Ca^{2+} current, I_T, underlying the low-threshold spike (LTS).

The prerequisite for the appearance of this rhythm is the hyperpolarization of TC neurons, generally to levels more negative than -65 or -70 mV. Thus, in contrast to the spindle oscillation that is generated by synaptic interactions in thalamic networks, which necessarily include RE nucleus, the delta oscillation is an intrinsic oscillation of TC neurons. The mechanisms of generation and synchronization of this thalamic oscillation were revealed using intracellular studies *in vitro* (46, 47, 48) and *in vivo* (21, 49).

The incompatibility between spindles and delta waves, which only occurs at the level of single neurons (and not at the EEG level), is due to the fact that these two rhythms appear at different membrane potentials of TC neurons. Around -60 mV, TC neurons display spindles, whereas at membrane potentials more negative than -65 or -70 mV spindles progressively decrease in amplitude and oscillations are within the delta frequency range. We have thus postulated a progressive hyperpolarization of TC cells with the deepening of NREM sleep, which is attributable to the progressive decrease in firing rates, during NREM sleep, of corticothalamic, midbrain core and mesopontine cholinergic neurons with thalamic projections, and some monoaminergic nuclei (52). It is also known from human and animal studies that spindles and delta waves prevail during different sleep stages and that these two rhythms reciprocally oscillate within NREM sleep (53, 54, 55). Conversely, at the end of NREM sleep, approaching REM sleep, when TC neurons become less hyperpolarized because of increased firing rates of mesopontine cholinergic neurons, which precede the onset of REM sleep and excite TC neurons (56), spindles are more obvious than during preceding epochs of deep NREM sleep.

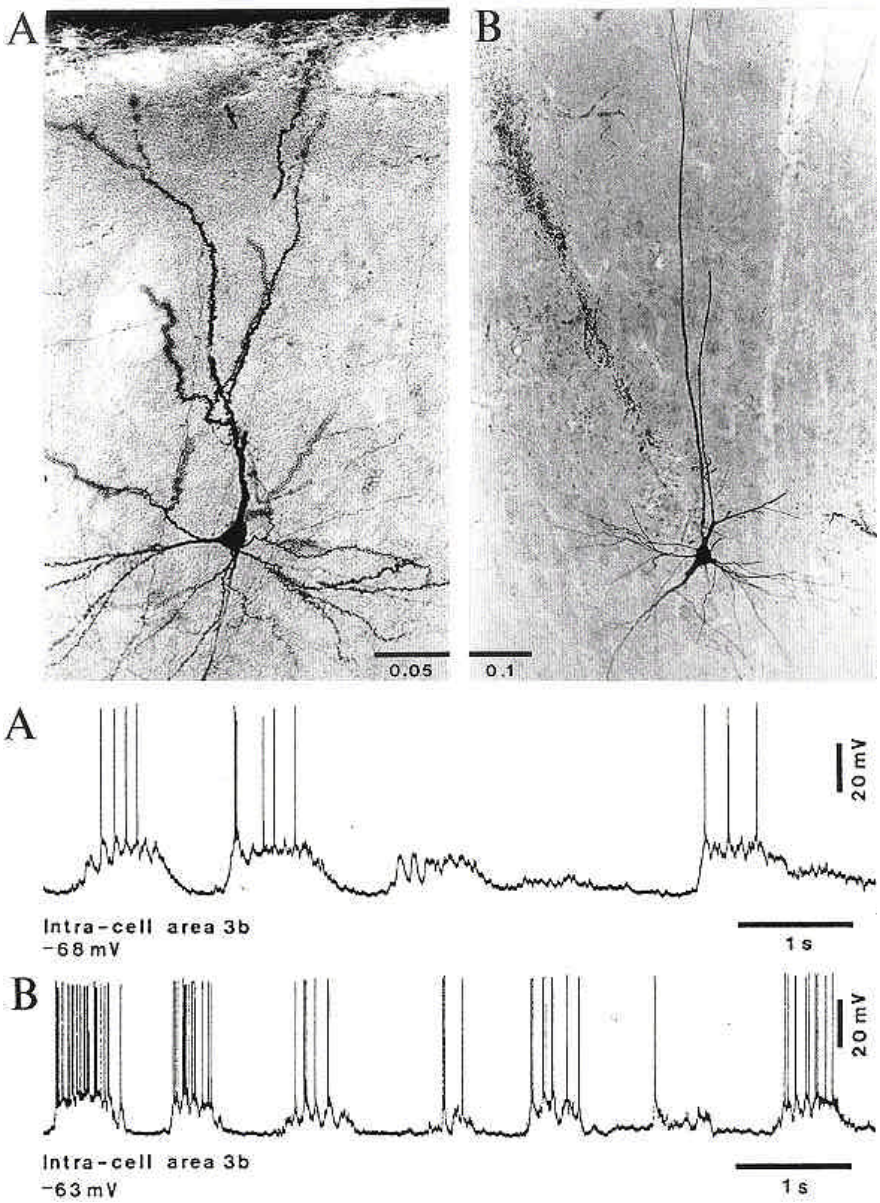

Figure 4. Intracellularly recorded and stained pyramidal neurons from cat primary somatosensory cortical display a slow oscillation. Ketamine-xylazine anesthesia. *A,* neuron at 0.3 mm from the surface (seen in the upper part of the photo) oscillated with periodic depolarizing-hyperpolarizing sequences at a frequency of about 0.6 Hz. This cell was extremely spiny and showed a prominent local arborization of its axon. Note oscillations within the frequency of spindle waves (10-12 Hz) during the depolarizing phase of the slow oscillation. *B,* pyramidal neuron at a depth of 1 mm, with two apical dendrites. Note the track left by the recording pipette on the left side of the cell. Both these neurons were regular-spiking cells. Modified from Contreras and Steriade (39).

Human studies of natural sleep, using EEG recordings in conjunction with regional cerebral blood flow (rCBF) studied with positron emission tomography (PET), concluded that delta activity covaried negatively with rCBF in the thalamus and brainstem reticular core, and that after the effect of delta was removed, an additional negative covariation (~35%) between spindles and the residual rCBF was still visible in the medial thalamus (57, 58). Again, these findings corroborate experimental data showing that spindles have a significant role in protecting the stability of sleep by disconnecting the subject from the outside world and may be a prerequisite for falling deeper asleep (see above).

Cortical volleys potentiate delta oscillation in TC cells by transforming subthreshold depolarizing waves into rhythmic LTSs crowned by fast Na^+ action potentials, which may persist for 10-20 seconds as a self-sustained activity, after cessation of cortical volleys (21). This synaptic action is mediated by thalamic RE GABAergic

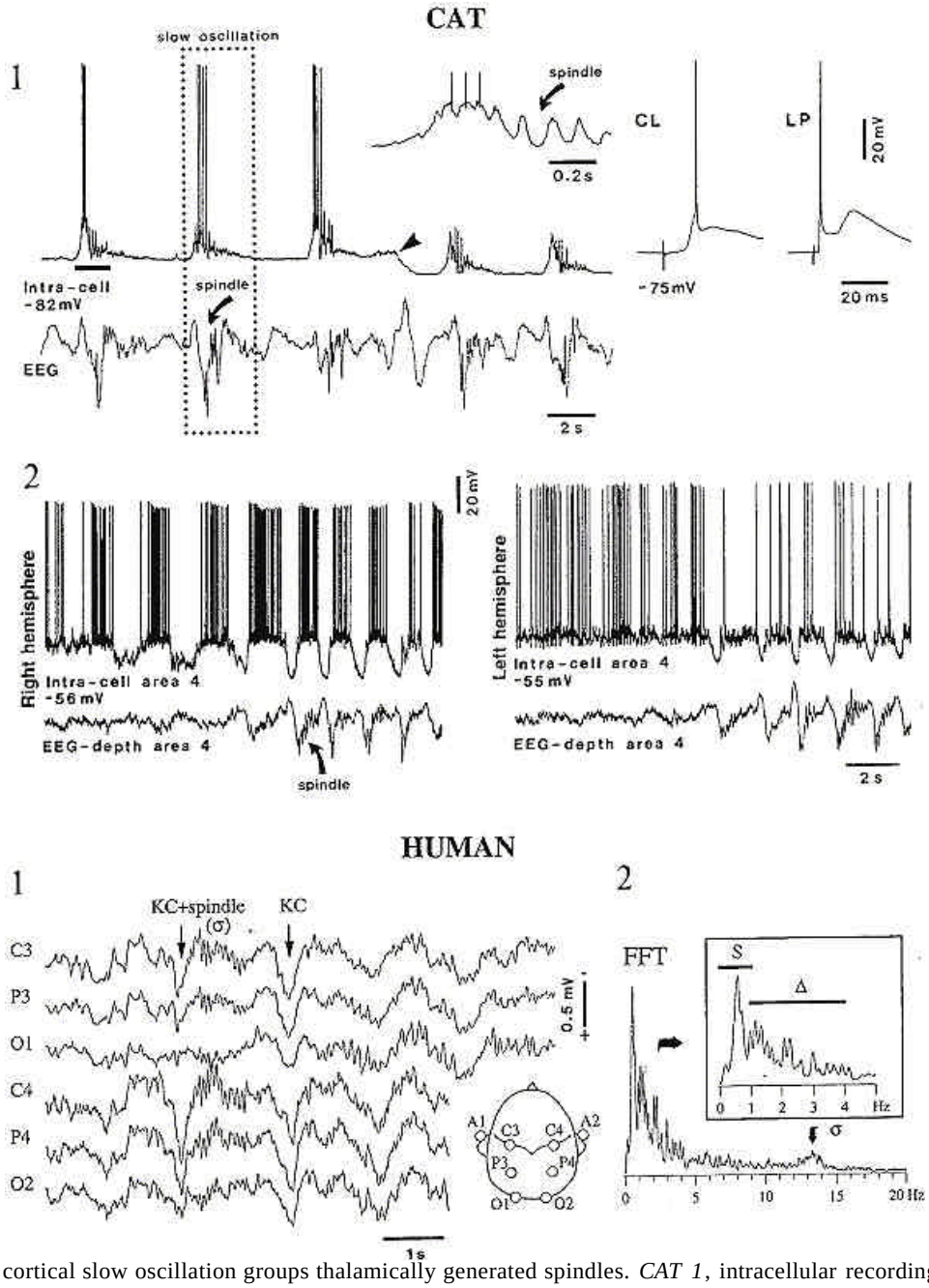

Figure 5. The cortical slow oscillation groups thalamically generated spindles. *CAT 1*, intracellular recording in cat under urethane anesthesia from area 7 (1.5 mm depth). Electrophysiological identification (at right) shows orthodromic response to stimulation of thalamic centrolateral (CL) intralaminar nucleus and antidromic response to stimulation of lateroposterior (LP) nucleus. Note slow oscillation of neuron and related EEG waves. One cycle of the slow oscillation is framed in dots. Part marked by horizontal bar below the intracellular trace (at left) is expanded above (right) to show spindles following the depolarizing envelope of the slow oscillation. *CAT 2*, dual simultaneous intracellular recordings from right and left cortical area 4. Note spindle during the depolarizing envelope of the slow oscillation and synchronization of EEG when both neurons synchronously display prolonged hyperpolarizations. *HUMAN*, the K-complex (KC) in natural sleep. Scalp monopolar recordings with respect to the contralateral ear are shown (see figurine). Traces show a short episode from a stage 3 non-REM sleep. The two arrows point to two K-complexes, consisting of a surface-positive wave, followed (or not) by a sequence of spindle (sigma) waves. Note the synchrony of K-complexes in all recorded sites. At right, frequency decomposition of the electrical activity from C3 lead (see A) into three frequency bands: slow oscillation (S, 0 to 1 Hz), delta waves (Δ, 1 to 4 Hz) and spindles (σ, 12 to 15 Hz). Modified from Steriade *et al.* (50 and 51, *CAT*) and from Amzica and Steriade (41, *HUMAN*).

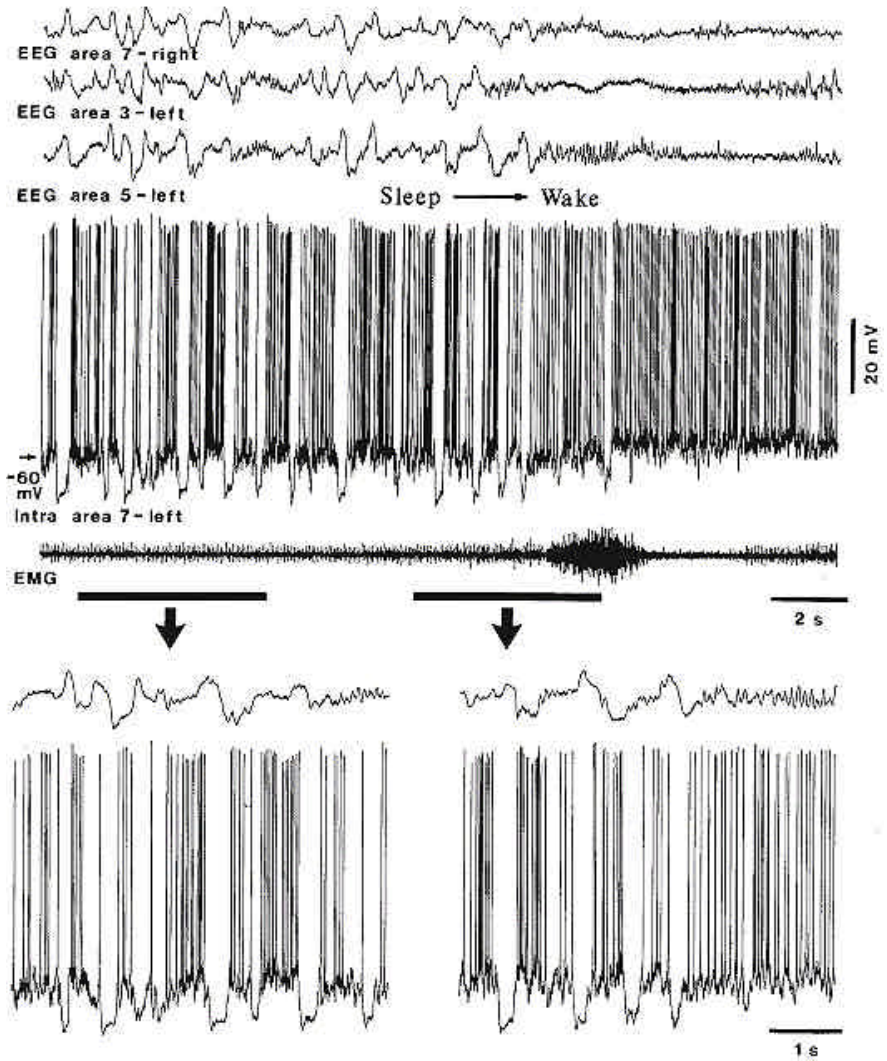

Figure 6. The slow oscillation during natural NREM (slow-wave) sleep (SWS) and its obliteration during transition to wakefulness. Chronically implanted cat. Five traces depict (from top to bottom): depth-EEG from right area 7 and left areas 3 and 5; intracellular activity of RS neuron from left area 7; and electromyogram (EMG). Two epochs marked by horizontal bars are expanded below (arrows). Cyclic hyperpolarizations characterize neocortical neurons during SWS, but their firing rate during the depolarizing phases of the slow sleep oscillation is as high as during the activated behavioral state of waking. Note phasic hyperpolarizations in area 7 neuron, related to depth-positive EEG field potentials, during SWS, tonic firing upon awakening marked by EEG activation and increased muscular tone, and slight depolarization occurring only after a few seconds after awakening and blockage of hyperpolarizations. Data from experiments by M. Steriade, I. Timofeev and F. Grenier [see also Steriade *et al.* (69)]

neurons, that set the membrane potential of TC neurons at the hyperpolarized level required for delta oscillations. Thus, an intrinsic property of TC cells is powerfully modulated by synaptic network operations.

The suppression of thalamic delta waves by activating cholinergic systems arising in the mesopontine nuclei is discussed below (see section 4). *(b)* That another delta component is generated in cortex is demonstrated by the presence of this activity after thalamectomy (50, 59). The mechanisms of cortical delta waves are much less understood than those underlying the clock-like thalamic delta rhythm. There is a relationship between the firing probability and surface-positive (depth-negative) delta waves, whereas the depth-positive waves are associated with a diminished discharge rate or even firing suppression (60) that is generated by summation of long-lasting afterhyperpolarizations (AHPs) produced by a variety of K^+ currents in deeply lying pyramidal neurons (61, 62). The decreased excitability that accompanies the slow AHP is consistent with the decreased synaptic and antidromic responsiveness of pyramidal tract and other corticofugal neurons during EEG epochs with delta waves (63).

3.3. The neocortical slow oscillation groups thalamically generated nrem sleep rhythms

The importance of the slow oscillation (<1 Hz, generally 0.5-1 Hz) resides in the fact that it groups other

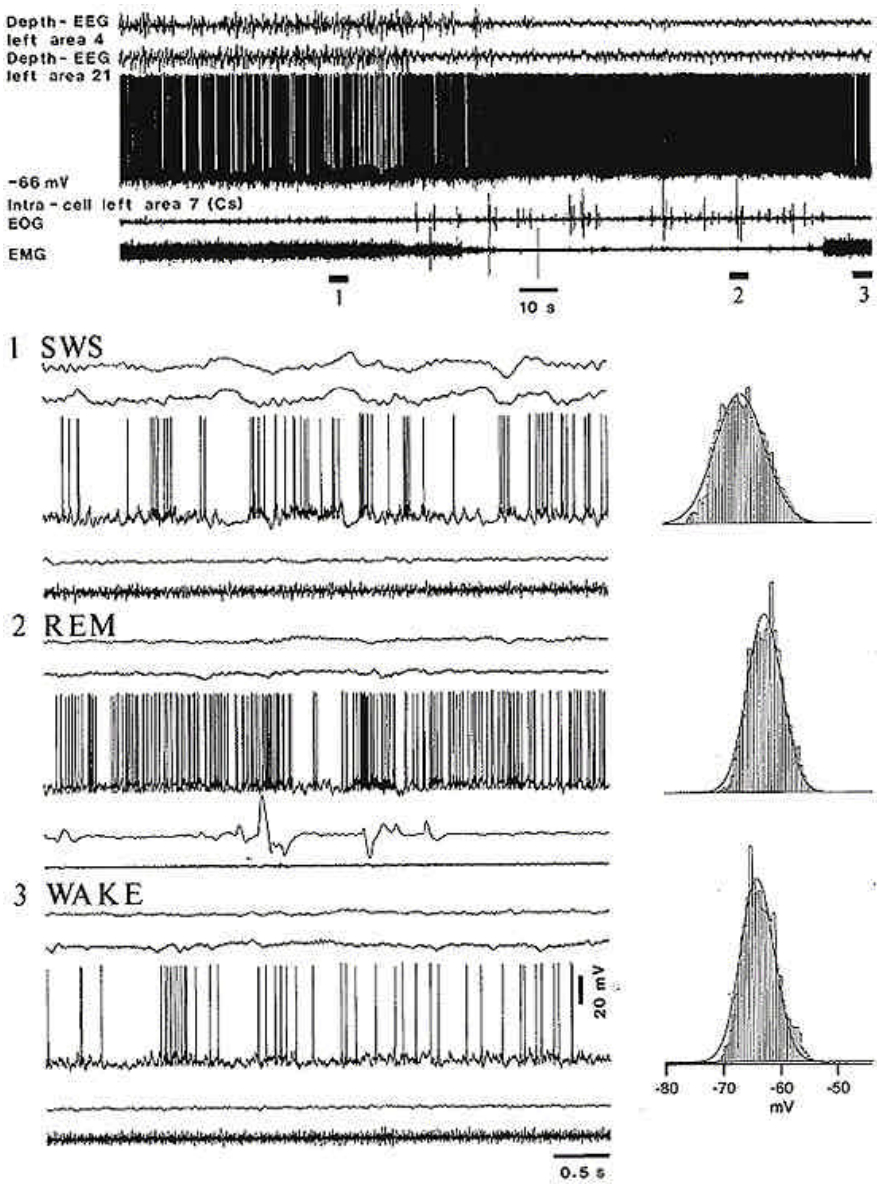

Figure 7. Prolonged hyperpolarizations of the slow oscillation during natural NREM (slow-wave) sleep (SWS) are reduced up to disappearance by recording intracellularly cortical neurons using micropipettes filled with Cs^+. Chronically implanted cat. Transition from NREM sleep to REM sleep. *Top* five traces are: depth-EEG recordings from left areas 4 and 21, intracellular recording from cortical neurons in left area 7 (Cs^+-filled pipette), electrooculogram (EOG) and electromyogram (EMG). Note muscular atonia and ocular saccades upon transition to REM sleep. Parts marked by horizontal bars below EMG trace and indicated by 1 (SWS), 2 (REM sleep) and 3 (waking), are expanded below. *Right,* histograms of membrane potential during the three states of vigilance (SWS, REM and waking). Note slightly more hyperpolarized membrane potential during SWS (compared to REM sleep and waking), but absence of a distinct hyperpolarizing tail that characterize SWS when intracellular recordings are made with K-acetate pipettes [see Steriade *et al.* (69) and Timofeev *et al.* (71)]. Compare prolonged and deep hyperpolarizations during SWS in the preceding Figure 6 with much reduced, almost absent hyperpolarizations in this record with Cs+-filled pipette. See also text. Data from experiments by M. Steriade, I. Timofeev and F. Grenier [see also Timofeev *et al*., (71)].

NREM sleep rhythms within complex wave-sequences (see below and Figure 5). The slow oscillation was first described using intracellular recordings from different neuronal types in anesthetized cats and, in the same article, was also detected in EEG recordings during natural NREM sleep in humans in which cyclic groups of delta waves at 1-4 Hz recurred with a slow periodicity, ~0.2-0.4 Hz (64). The grouping of these two oscillatory types, within frequency bands of 1-4 Hz and 0.3-1 Hz, is one of the arguments supporting the distinctness between delta and slow sleep oscillations. Another argument came from human studies (65) showing that the typical decline in delta

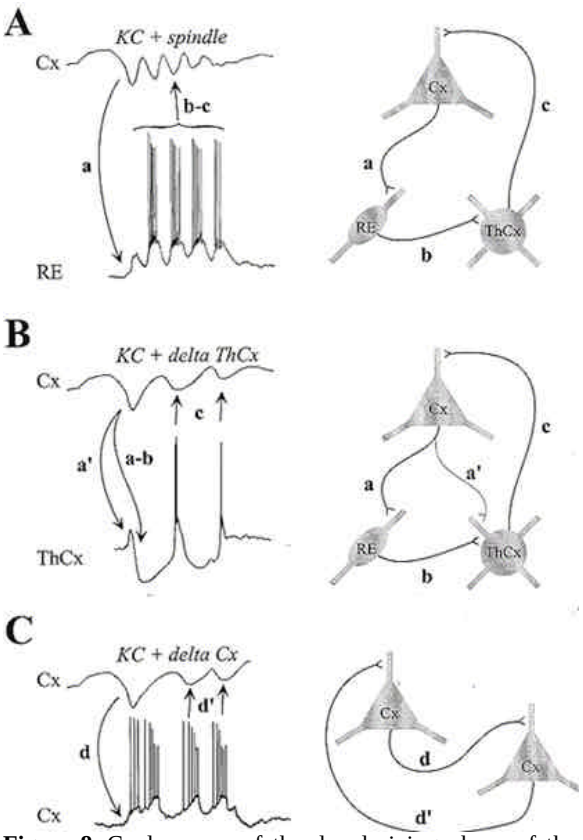

Figure 8. Coalescence of the depolarizing phase of the slow oscillation (K-complex, KC) with other sleep rhythms. In the left column, field potential and intracellular recording. In the right column, scheme of the circuit involved in the generation of the respective EEG pattern. The synaptic projections are indicated with small letters, corresponding to the arrows at left, which indicate the time sequence of the events. *A*, combination of a KC with a spindle sequence. A KC in the cortex (*Cx*) travels through the corticothalamic pathway (*a*) and triggers in the thalamic RE nucleus (*RE*) a spindle sequence that is transferred to thalamocortical cells (*ThCx*) of the dorsal thalamus (*b*) and thereafter back to the cortex (*c*) where it shapes the tail of the KC. *B*, modulation of a KC by a sequence of clock-like delta waves originating in the thalamus. The KC travels along the corticothalamic pathway (*a'*) eliciting an EPSP curtailed by an IPSP produced along the cortico-RE (*a*) and RE-ThCx (*b*) projections. The hyperpolarization of the thalamocortical cell generates a sequence of low-threshold potentials crowned by high-frequency spike-bursts at delta frequency that may reach the cortex through the thalamocortical link (*c*). *C*, modulation of a KC by a sequence of delta waves originating in the cortex. When the KC impinges upon bursting cells (*d*) it triggers a series of rhythmic bursts of spikes at delta frequency that may have a greater impact on target cells (*d'*) than single action potentials, thus synchronizing several neurons whose membrane potentials will be reflected in local field potentials as delta waves. From Amzica and Steriade (98).

activity (1-4 Hz) from the first to the second NREM sleep episode was not present at frequencies characteristic for the slow oscillation (range 0.55-0.95 Hz).

The cortical nature of the slow oscillation was demonstrated by its survival in the cerebral cortex after thalamectomy (50) and presence in isolated large cortical slabs *in vivo* (66) or cortical slices maintained *in vitro* (67); its absence in the thalamus of decorticated animals (40); and the disruption of its long-range synchronization after disconnection of intracortical synaptic linkages (68).

The slow oscillation was recorded in all major types of neocortical neurons, including pyramidal-shaped and local-circuit inhibitory neurons, as identified electrophysiologically and by intracellular staining (Figure 4). This oscillation is made up by a prolonged depolarizing phase, followed by a long-lasting hyperpolarization (Figure 4). In intracellular recordings from cortical neurons in chronically-implanted, naturally sleeping animals, the slow oscillation with clear-cut hyperpolarizing phases appears from the very onset of NREM sleep (69).

The depolarizing phase consists of non-NMDA-mediated EPSPs, fast prepotentials (FPPs), a voltage-dependent persistent Na^+ current ($I_{Na(p)}$), and fast IPSPs reflecting the action of synaptically coupled GABAergic local-circuit cortical cells (64).

At a first sight, the hyperpolarizing phase of the slow oscillation might be ascribed to the action of local inhibitory neurons. However, the hyperpolarized phase of the slow oscillation in neocortical neurons was demonstrated to be due to disfacilitation (removal of synaptic, mainly excitatory, inputs) in intracortical and thalamocortical networks (70), and to some K^+ currents (71), but not to active inhibitory processes. Indeed, neurons identified electrophysiologically as fast-spiking cells and morphologically as basket, aspiny cells, during anesthesia (39) and natural NREM sleep (69), behave in phase with regular-spiking (pyramidal) neurons, namely, they fire during the depolarizing phase and are silent during the hyperpolarizing phase. Also, intracellular recordings with Cl^--filled pipettes during naturally sleeping animals did not affect the prolonged hyperpolarizations of the slow oscillation in NREM sleep (69, 71). Recordings with Cs^+-filled pipettes reduced and often abolished the hyperpolarizing phase of the slow oscillation (71; see also below, Figure 7), thus leading to the conclusion that the hyperpolarizations during the slow oscillation are, at least partially, produced by a series of K^+ currents, most probably $I_{K(Ca)}$. In support of this assumption, stimulation of cholinergic afferents blocks selectively the prolonged hyperpolarizations, even without changes in membrane potential (72), and acetylcholine (ACh) increases the excitability of cortical neurons by reducing some voltage- and Ca^{2+}-dependent K^+ currents (73, 74). As to the disfacilitation factor, it might be explained by a progressive depletion of $[Ca^{2+}]_o$ during the depolarizing phase of the slow oscillation (75), which would produce a decrease in synaptic efficacy and an avalanche reaction that would

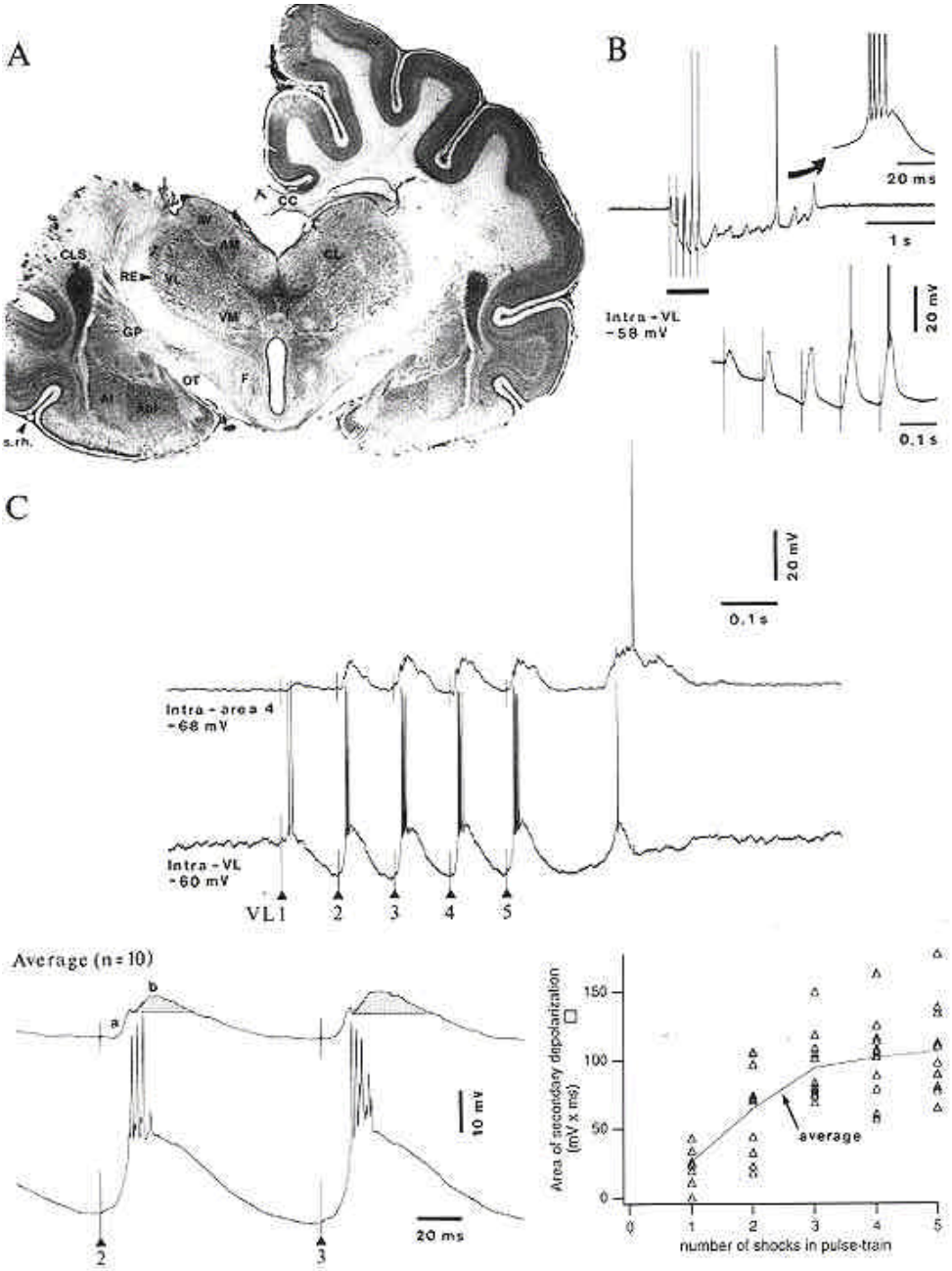

Figure 9. Augmenting responses in thalamic neurons and in TC systems. A, hemidecortication (ipsilateral to thalamic recordings) and cut of corpus callosum. Nissl-stained section. Abbreviations: AV, AM, CL, RE, VL and VM, anteroventral, anteromedial, centrolateral, reticular, ventrolateral and ventromedial thalamic nuclei; CA, caudate nucleus; CC, corpus callosum; F, fornix; Al and Abl, lateral and basolateral nuclei of amygdala; CLS, claustrum; GP, globus pallidus; OT, optic tract; s.rh., rhinal sulcus (arrowhead). B, intrathalamic augmenting responses in decorticated cat (see A). Intracellular recordings from the thalamic ventrolateral (VL) nucleus under ketamine-xylazine anesthesia show low-threshold augmenting responses of VL cell developing from progressive increase in IPSP-rebound sequences and followed by a self-sustained spindle. Arrow indicates expanded spike-burst (action potentials truncated). The part marked by horizontal bar and indicating augmenting responses is expanded at right. C, dual simultaneous intracellular recording from cortical area 4 and thalamic VL nucleus in cat under ketamine-xylazine anesthesia. Below, average of 2nd and 3rd responses in cortical and VL cells. The area of secondary depolarization in cortical neuron (b), which develops during augmentation, is marked by dots. During thalamically-evoked augmenting responses, the cortical augmented component (secondary depolarization, b) follows the rebound spike-burst in TC neuron, and the depolarization area in cortical neuron increases as a function of number of action potentials in the rebound spike-burst of TC cell. Right plot, area of secondary depolarization of cortical cell as a function of the number of stimuli in the pulse-trains (the line represents the mean). Modified from Steriade and Timofeev (94; A-B) and Steriade *et al.* (92; panel C).

eventually lead to the functional disconnection of cortical networks.

The depolarizing and hyperpolarizing envelopes of the slow oscillation were also observed in cortical glial cells, with a different time-course than the simultaneously impaled neurons (76, 77). This suggested a possible role of glia in pacing normal oscillatory activities and in the development from sleep rhythms to seizure episodes.

Unlike "pure" rhythms within distinct frequency bands, generated in restricted circuits of extremely simplified preparations, such as slices maintained *in vitro*, the living brain does not generally display separate oscillations during NREM sleep, but a coalescence of slow oscillation with other sleep rhythms as well as with fast rhythms (superimposed on the depolarizing phase). The latter are conventionally thought to define brain-activated states of waking and REM sleep but they also appear, with lower incidence, during NREM sleep. During the depolarizing envelope of the slow oscillation, the synchronous firing of neocortical neurons impinges upon thalamic RE neurons, thus creating conditions for formation of spindles, transferring them to TC systems. This connectivity and its functional features explain why a cycle of the slow oscillation is followed by a brief sequence of spindles in TC neurons as well as in the cortical EEG. This was seen with single and dual intracellular recordings from anesthetized and naturally sleeping animals, as well as in the EEG recordings from human NREM sleep (41, 50, 69) (Figure 5). The sequence of grapho-elements consisting of an ample surface-positive transient, corresponding to the excitation in deeply lying cortical neurons, followed by a slower, surface-negative component and eventually a few spindle waves, represents this combination between the slow and spindle oscillation, and is usually termed the K-complex (Figure 5, *HUMAN*). This is a reliable sign for stage 2 of human sleep, but it is apparent in all stages of NREM sleep. Through their shape, K-complexes contain spectral components belonging to the delta band.

The slow oscillation, mainly discovered with single and dual intracellular recordings under anesthesia, was recently observed, with the same features, using intracellular recordings during all natural sleep states and during shifts from NREM sleep to waking (Figure 6) or REM sleep (Figure 7).

The powerful effects exerted by the slow sleep oscillation became obvious by recording the same type of rhythm in distant structures (such as the thalamus, basal ganglia, nucleus basalis and some brainstem structures), in which the slow oscillation disappeared after reversible inactivation or ablation of neocortex (40, 50, 78-81). The effects of slowly oscillating corticothalamic neurons lead to the grouping of other sleep oscillations, generated in the thalamus. This is illustrated in Figure 8 showing how the depolarizing component of the cortical slow oscillation generates thalamic spindles (panel *A*), thalamic clock-like delta waves (panel *B*), and cortical delta waves (panel *C*). In addition, the depolarizing phase of the cortical slow sleep oscillation is associated with the presence of fast (82, 83) and ultra-fast (84) rhythms, which are voltage-dependent.

3.4. NREM low-frequency oscillations and corticothalamic plasticity

Far from being epiphenomena with no functional significance, spontaneously occurring brain rhythms during NREM sleep produce plastic changes in neuronal responsiveness. Although earlier hypotheses postulated that NREM sleep is associated with a global cortical inhibition (85) that prevents any mental activity and produces "abject mental annihilation" (86), neocortical neurons display an unexpectedly rich spontaneous activity under some anesthetics and during natural NREM sleep (69). This indicates that the neocortex is quite active during NREM sleep and suggests a reorganization/specification of neuronal circuits in cortex and target structures (87). Our view is supported by studies using indicators of neuronal activities during NREM sleep in humans, revealing more marked changes in those neocortical areas that are implicated in memory tasks and decision-making during wakefulness (88).

I shall briefly focus on the role of sleep spindles and their experimental model (augmenting responses) in producing plastic changes in neuronal properties through rhythmic repetition, at an optimal frequency range of ~10 Hz, of spike-bursts and spike-trains in thalamic and cortical neurons. Although augmenting potentials have been studied since the 1940s (89), intracellular recordings of these responses and detailed analyses of their mechanisms have only been performed during the past few years, in studies on the rat and cat sensorimotor and association cortices (90, 91, 92, 93) as well as in the thalamus of decorticated cats (94, 95). Realistic models of the augmentation phenomenon provided insights into the mechanisms of augmenting responses and made predictions that could be further tested experimentally (96, 97).

Both the thalamus and the cerebral cortex have the neuronal machinery that is necessary to generate incremental responses. In decorticated animals, TC neurons display two forms of augmenting responses in response to 10-Hz local stimulation: low-threshold augmenting, expressed by progressively *increased IPSPs* and rebound spike-bursts (Figure 9*A-B*); and high-threshold augmenting, associated with progressively *decreased IPSPs* and progressive depolarization of neurons leading to high-threshold spike-bursts (Figure 10*A*). However, the full consequences of the augmenting phenomenon, which include self-sustained oscillations and plastic changes in network activities, eventually leading to paroxysmal episodes, are not observed in the thalamus of decorticated animals or in the isolated cortex, but they require intact connections in the reciprocal thalamocorticothalamic loops. In these experimental conditions, which are characterized by intact brain connectivity, the secondary depolarization, which characterizes the augmenting phenomenon, constantly follows the beginning of spike-bursts in thalamocortical neurons by a few milliseconds (Figure 9*C*).

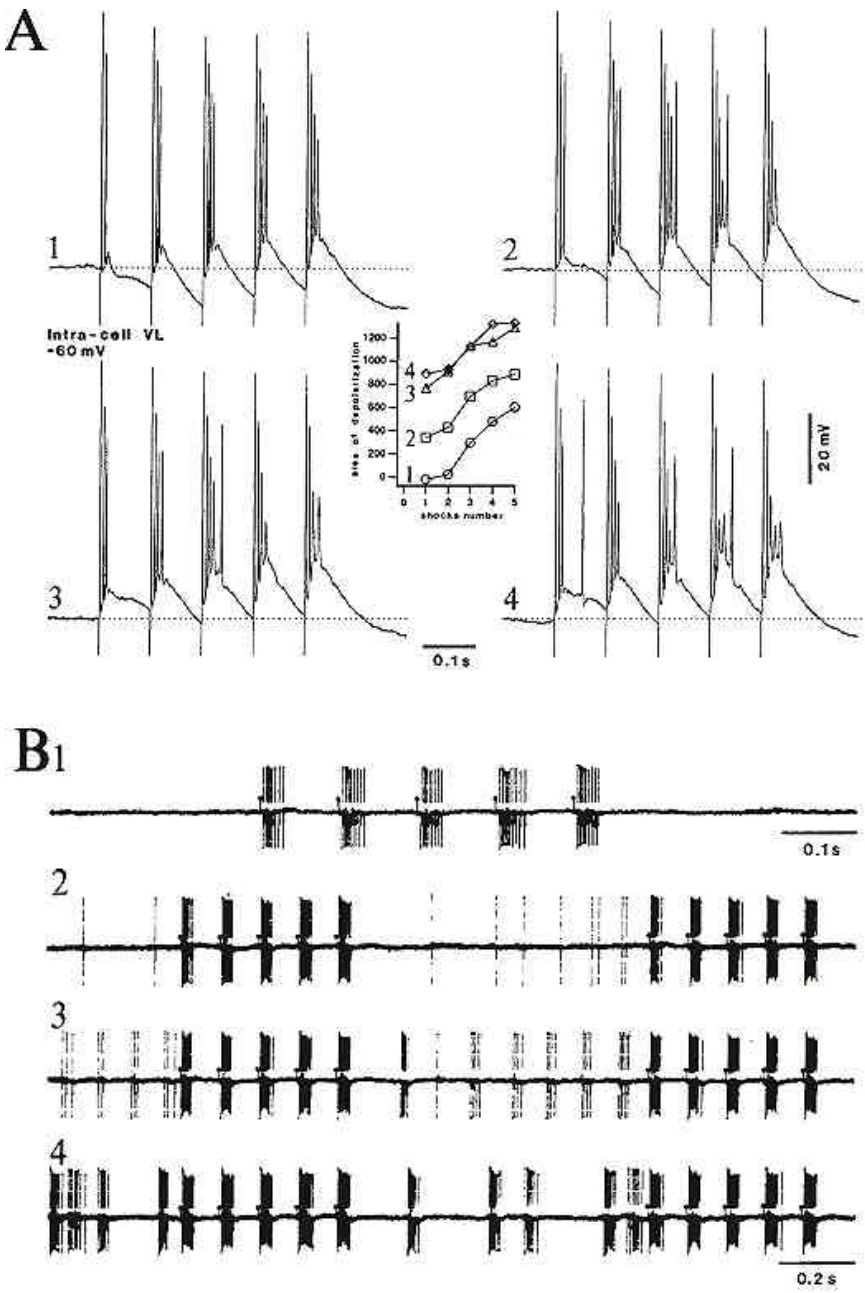

Figure 10. Short-term plasticity from repetitive intrathalamic augmenting responses of the high-threshold type, and development from corticothalamic augmenting responses to self-sustained activity. *A,* intracellular recording of thalamic VL neuron in cat with ipsilateral hemidecorticaion and callosal cut (as in Figure 9*A*). Ketamine-xylazine anesthesia. Progressive and persistent increase in the area of depolarization by repeating the pulse-trains. Pulse-trains consisting of 5 stimuli at 10 Hz were applied to the VL every 2 sec. The VL cell was recorded under +0.5 nA (-60 mV); at rest, the membrane potential was -72 mV. Responses to four pulse-trains (*1-4*) are illustrated (*1* and *2* were separated by 2 sec; *3* and *4* were also separated by 2 sec and followed 14 sec after *2*). The responses to 5-shock train consisted of an early antidromic spike, followed by orthodromic spikes displaying progressive augmentation and spike inactivation. Note that, with repetition of pulse-trains, IPSPs elicited by preceding stimuli in the train were progressively reduced until their complete obliteration and spike-bursts contained more action potentials with spike inactivation. The graph depicts the increased area of depolarization from the first to the fifth responses in each pulse-train as well as from pulse-train *1* to pulse-trains *3* and *4*. *B,* brainstem-transected cat. Cortically evoked spike-bursts in thalamic VL neuron (*1*). Motor cortex stimulation was applied with pulse-trains at 10 Hz delivered every 1.3 seconds. In *1*, the pattern of cortically evoked responses at the onset of rhythmic pulse-trains (faster speed than in *2* to *4*). *2-4*, responses at later stages of stimulation. Stimuli are marked by dots. In *2* to *4*, stimuli and evoked spike-bursts are aligned. Note progressive appearance of spontaneous spike-bursts resembling the evoked ones, as a form of "memory" in the corticothalamic circuit. Modified from Steriade and Timofeev (94; *A*) and Steriade (7; *B*).

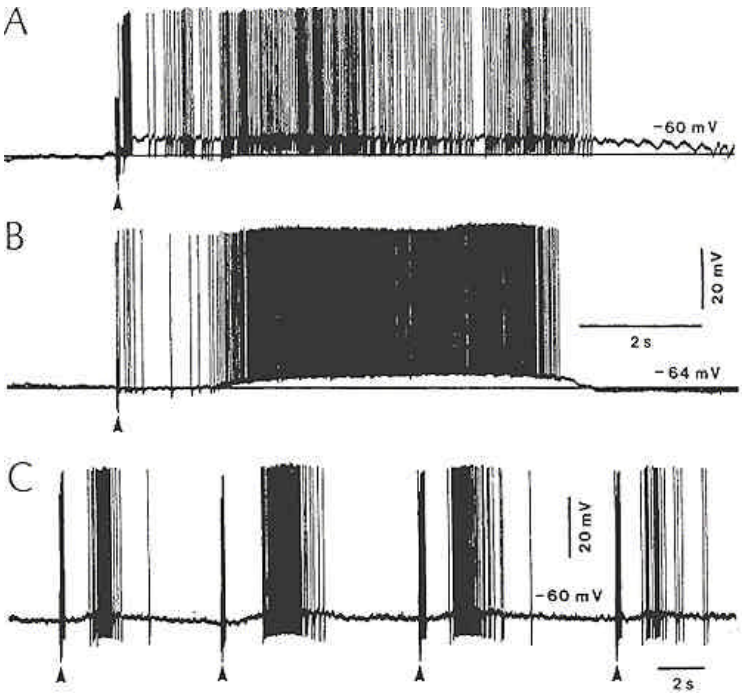

Figure 11. Direct excitation of lateral geniculate (LG) thalamic nucleus by stimulating the pedunculopontine tegmental (PPT) cholinergic nucleus. Intracellular recordings in *encéphale isolé* unanesthetized cat, with deafferentation of trigeminothalamic pathways; visual cortex and retinal were also removed to prevent the occurrence of spontaneous EPSPs. *A-B*, a few stimuli to the PPT (arrowheads) elicited a short-latency excitation followed by a long-latency (1-1.5 s) and prolonged (1.5-2.5 s) excitation. *C*, a series of successive PPT-evoked responses (early and late excitations) at a lower speed. Data from unpublished experiments by B. Hu, M. Deschênes and M. Steriade [see Steriade and Deschênes (45)].

This succession of events indicates the dependence of cortical incremental responses on intrathalamic processes, particularly the low-threshold type of augmentation.

Augmenting responses are associated with short-term plasticity processes, that is, persistent and progressive increases in depolarizing synaptic responses (Figure 10*A*) and decreases in inhibitory responses. Repeated spike-bursts evoked by volleys applied to corticothalamic pathways or occurring during spontaneous oscillations may lead to self-sustained activity patterns, resembling those evoked in the late stages of stimulation (Figure 10*B*). Such changes are due to resonant activities in closed loops, as in "memory" processes. The repeated circulation of impulses in reverberating circuits, especially when considering those corticothalamic neurons that are able to discharge rhythmic spike-bursts (99), could lead to synaptic modifications in target structures, which favor alterations required for memory processes. It was indeed shown that the overnight improvement of visual discrimination tasks requires some steps depending on the early part of NREM sleep (100). The improvement of visual discrimination skills by early stages of NREM sleep led to the conclusion that procedural memory formation is prompted by NREM sleep (101). It was suggested that the massive Ca^{2+} entry in cortical pyramidal cells during sleep spindles activates a molecular "gate" mediated by protein kinase A and that this process could allow permanent changes to subsequent inputs following sleep spindles (102).

4. BRAIN ACTIVATION AND FAST RHYTHMS DURING WAKING AND REM SLEEP

Two parallel pathways arise from mesopontine (pedunculopontine and laterodorsal tegmental, PPT/LDT) nuclei to activate the thalamus and cerebral cortex during waking and REM sleep. The dorsal path uses ACh as neurotransmitter to TC neurons that, in turn, release glutamate at the cortical level. The ventral projection activates nucleus basalis (NB) neurons. Since ACh inhibit NB cells (103), PPT/LDT neurons activate NB cells through glutamate (104) that is co-localized with ACh in many PPT/LDT cells (105). The presence of these two parallel activating pathways is supported by experiments showing that brainstem-induced depolarization of cortical neurons, their enhanced excitability, and replacement of low-frequency oscillations by fast rhythms in the beta (~20-30 Hz) and gamma (~30-60 Hz) frequency range, can be achieved after extensive ipsilateral lesions of either thalamus or NB (72, 106). Thus, either PPT/LDT or NB cholinergic nuclei are sufficient to activate the cerebral cortex, NB through direct projections, PPT/LDT nuclei through a synaptic linkage in diffusely projecting thalamic nuclei. Indeed, bilateral lesions of thalamic intralaminar nuclei lead to prolonged lethargy and somnolence (107).

The direct PPT/LDT projection to TC neurons in felines and primates (108, 109) produces a powerful excitation at their targets (Figure 11). The muscarinic

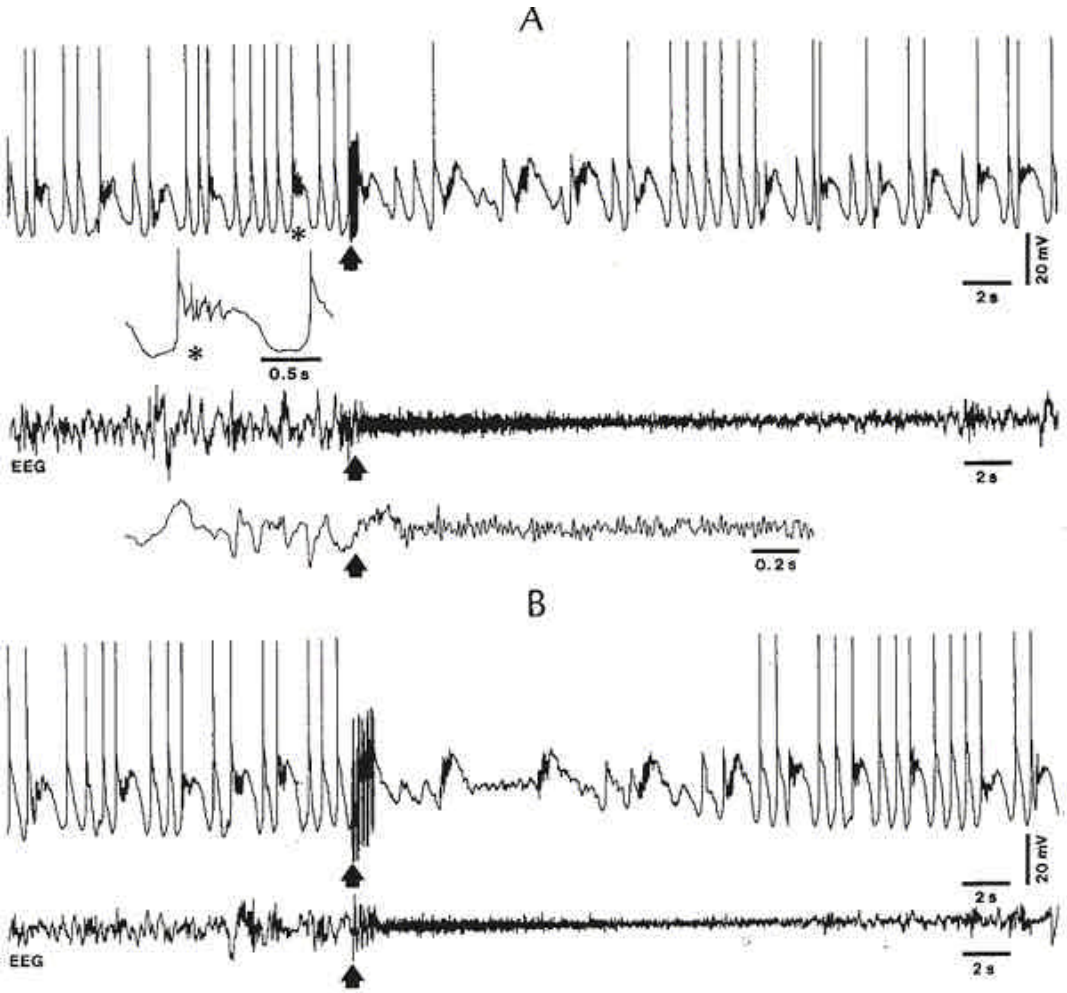

Figure 12. Suppression of the clock-like delta oscillation in a thalamocortical (TC) neuron of cat by stimulation of the pedunculopontine tegmental (PPT) nucleus, and simultaneous cortical activation with the appearance of fast (~40 Hz) activity. Intracellular recording from TC cell in the lateroposterior (LP) nucleus, together with EEG from postcruciate gyrus. *A*, a pulse-train to the PPT nucleus reduced the rhythmic (~2 Hz) low-threshold spikes crowned by fast action potentials in TC cell and, simultaneously, induced fast EEG activity. Part marked by asterisk in the intracellular trace is expanded below to show postsynaptic potentials (PSPs) whose origin is the slow cortical oscillation. The EEG before and after the PPT train is expanded below to show ~40 Hz activity induced by PPT stimulation. *B*, stronger effects were induced by 5 pulse-trains to PPT nucleus, which completely blocked the clock-delta oscillation of TC cell for ~15 seconds, and simultaneously produced a long-lasting EEG activation. From Steriade *et al*. (21).

component of this prolonged depolarization is associated with an increase in input resistance (19), which explains the increased responsiveness of TC neurons during brain-activated states of waking and REM sleep (110).

PPT/LDT neurons exhibit increased activity preceding the first gross electrographic signs of waking and REM sleep (56) and generate many types of ponto-geniculo-occipital (PGO) potentials (111), a cardinal sign of REM sleep. These features make mesopontine cholinergic nuclei the best candidates to generate activation processes in TC systems. One should emphasize, however, that non-cholinergic neurons are much more numerous than the cholinergic ones in the brainstem reticular core and some of them are glutamatergic (112). In the upper midbrain reticular formation, where there are virtually no cholinergic neurons, thalamically projecting, presumably glutamatergic neurons display precursor signs of increased activity during shifts from NREM sleep to either wakefulness or REM sleep (113). Some glutamate-induced excitatory actions consist in depolarization and increased input resistance of TC neurons, similarly to the effects exerted by ACh, as both these neurotransmitters block a "leak" K^+ current [reviewed in Steriade *et al*. (9)].

The activation processes in TC systems consist of the blockage of synchronized low-frequency oscillations that are typical for NREM sleep and the generation of fast (beta/gamma) rhythms that characterize the spontaneous activity during waking and REM sleep.

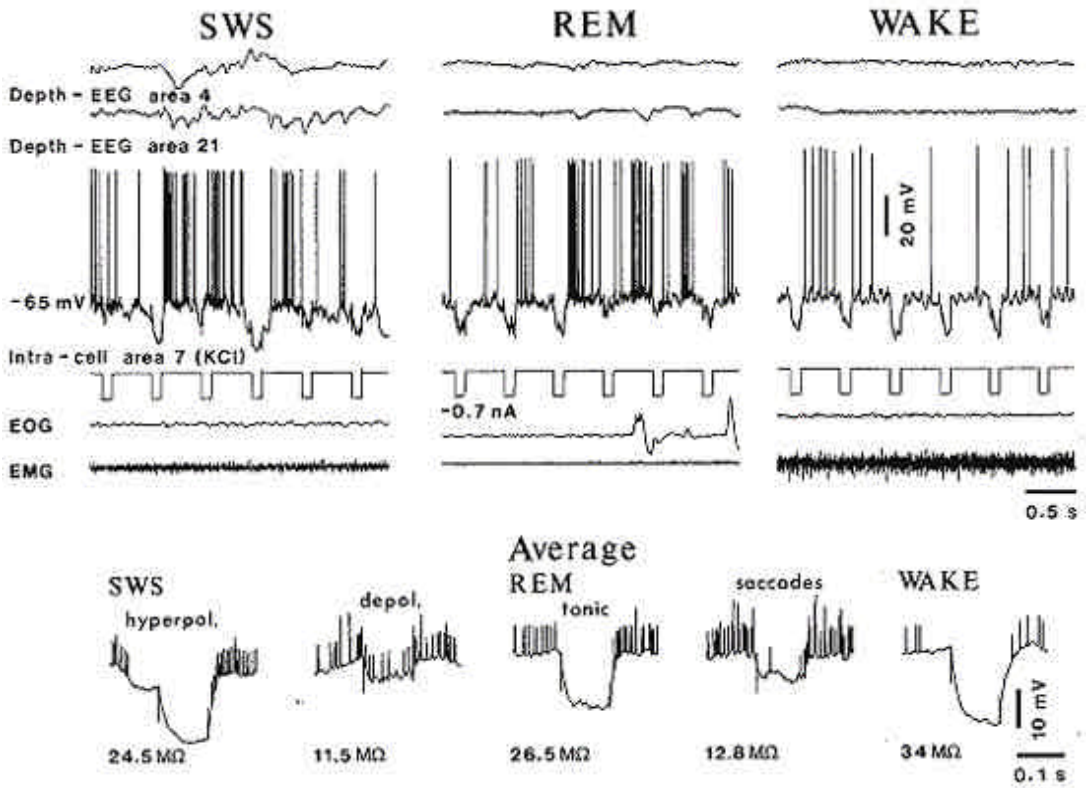

Figure 13. Apparent input resistance (R_{in}) of neocortical neurons during natural states of vigilance in chronically implanted cat. Upper panel shows three periods of intracellular recording from the same regular-spiking (RS) neuron during NREM (slow-wave) sleep (SWS), REM sleep and waking. R_{in} was measured by applying 0.1-s hyperpolarizing current pulses, every 0.5 s. Below, averages of responses of this neuron during different epochs in the three states of vigilance (note differences between the hyperpolarizing and depolarizing phases of the slow oscillation in SWS; and between epochs with and without ocular saccades in REM; see text). Modified from Steriade *et al*. (69).

The obliteration of thalamic sleep spindles and clock-delta oscillation is produced by PPT/LDT-inhibition of spindles' pacemaker, the RE nucleus, and by the depolarization of TC neurons (see Figure 1), thus bringing TC neurons out of the voltage range at which clock-like delta rhythm is generation (Figure 12). The erasure of cortically generated slow oscillation upon arousal is explained by the actions of PPT/LDT or NB nuclei that selectively block the hyperpolarizing phase of this oscillation, even without changes in membrane potential (72). These are the "negative" signs of brain activation. The "positive" event is the generation of fast oscillations that are voltage-dependent, i.e. can be elicited by depolarizing current steps in TC (106) as well as neocortical (114-116) neurons. Thus, there is no surprise that such fast oscillations (20-60 Hz) appear on the depolarizing phase of the slow oscillation in NREM sleep and, in a more sustained manner, throughout waking and REM sleep, states whose spontaneous activity of neocortical neurons is devoid of prolonged hyperpolarizations (69).

The apparent input resistance (R_{in}) is a measure resulting from passive electrical neuronal properties and balanced changes in excitatory and inhibitory inputs from specific and modulatory pathways. It may be predicted a decreased input resistance of neocortical neurons with increases in synaptic inputs during active states of waking and REM sleep when so many conductances are open due to inputs from other cortical and TC cells as well as generalized activating systems. However, in contrast to the two sleep (NREM and REM) states, the R_{in} is remarkably stable during the steady state of waking and it reaches higher values (31.3 ± 2.4 MΩ) than during the depolarizing phase of the slow oscillation in NREM sleep (16.8 ± 2.3 MΩ) (69) (Figure 13). The increased R_{in} during wakefulness may be related to earlier extracellular recordings showing an enhanced antidromic and synaptic responsiveness of monkey's neocortical neurons during this behavioral state, compared to slow-wave sleep (63). The result of an increased R_{in} during waking may be explained by increased release of ACh in cortex during brain activation (117) and the fact that ACh released during brain-active states increases the R_{in} of cortical neurons (73).

5. CONCLUDING REMARKS

During NREM sleep, the neuronal patterns in corticothalamic systems are reorganized. The sustained, single-spike activity observed during both waking and REM sleep develops into a burst-silence mode that characterizes all three NREM sleep rhythms: spindles, delta and slow oscillation. The slow oscillation of

corticothalamic neurons has the virtue of grouping other NREM sleep rhythms, generated within the thalamus. Thus, in intact-brain animals, there are no "pure" oscillatory types, generated in simple neuronal circuits. While the prolonged periods of hyperpolarizations, some of them associated with increased membrane conductance, ensures brain disconnection from the outside world and provides a well-deserved rest, other components of NREM sleep oscillations are factors that favor an active role of NREM sleep in the consolidation of memory traces acquired during wakefulness. During the depolarizing phase of the slow oscillation, cortical neurons fire as intensely as during waking and REM sleep, and generate fast oscillations of the beta/gamma type. And, through their rhythmic spike-bursts, spindles or their experimental model (augmenting responses in thalamocorticothalamic loops) produce synaptic plasticity at their targets and resonance phenomena, as in "memory" processes.

6. ACKNOWLEDGEMENTS

Personal experiments discussed in this article are supported by grants from the Canadian Institutes for Health Research (MT-3689 and MOP-36545), Natural Sciences and Engineering Research Council of Canada (170538), Human Frontier Science Program (RG0131), and National Institute of Health of United States (NINDS, 1-R01 NS40522-01).

I thank the following Ph.D. students and postdoctoral fellows for their fruitful collaboration in experiments performed during recent years (in order of appearance in my laboratory): D. Paré, R. Curró Dossi, A. Nuñez, F. Amzica, D. Contreras, I. Timofeev, D. Neckelmann and F. Grenier. Collaboration with T.J. Sejnowski, A. Destexhe, M. Bazhenov and W.W. Lytton was instrumental in computational studies. P. Giguère had a decisive role in the technical development of my laboratory.

7. REFERENCES

1. Krueger J M, J. R. Pappenheimer & M. L. Karnovsky: Sleep-promoting effects of muramyl peptides. *Proc Natl Acad Sci USA* 79, 6102-6106 (1982)

2. Borbély A A & I. Tobler: Endogenous sleep-promoting substances and sleep regulation. *Physiol Rev* 69, 605-670 (1989)

3. Steriade M, G. Iosif & V. Apostol: Responsiveness of thalamic and cortical motor relays during arousal and various stages of sleep. *J Neurophysiol* 32, 251-265 (1969)

4. Timofeev I, D. Contreras & M. Steriade: Synaptic responsiveness of cortical and thalamic neurons during various phases of slow oscillation in cat. *J Physiol (Lond)* 494: 265-278 (1996)

5. Elton M, O. Winter, D. Heslenfeld, D. Loewy, K. Campbell & A. Kok: Event-related potentials to tones in the absence and presence of sleep spindles. *J Sleep Res* 6, 78-83 (1997)

6. Hirsch J C, A. Fourment & M. E. Marc: Sleep-related variations of membrane potential in the lateral geniculate body relay neurons of the cat. *Brain Res* 259, 308-312 (1983)

7. Steriade M: Alertness, quiet sleep, dreaming. In: *Cerebral Cortex* (vol. 9, *Normal and Altered States of Function*) Eds: Peters A, Jones E G, Plenum, NY, 279-357 (1991)

8. Steriade M, E. G. Jones & R. R. Llinás: *Thalamic Oscillations and Signaling.* Wiley-Interscience, New York (1990)

9. Steriade M, E. G. Jones & D. A. McCormick: *Thalamus* (vol. 1, *Organisation and Function*) Elsevier, Oxford (1997)

10. Steriade M, E.G. Jones & D. A. McCormick (Eds): *Thalamus* (vol. 2, *Experimental and Clinical Aspects*) Elsevier, Oxford (1997)

11. Golshani P, X. B. Liu & E. G. Jones: Differences in quantal amplitude reflect GluR4-subunit number at corticothalamic synapses on two populations of thalamic neurons. *Proc Natl Acad Sci USA* 98, 4172-4177 (2001)

12. Steriade M, L. Domich & G. Oakson: Reticularis thalami neurons revisited: activity changes during shifts in states of vigilance. *J Neurosci* 6, 68-81 (1986)

13. Steriade M & D. Contreras: Relations between cortical and thalamic cellular events during transition from sleep pattern to paroxysmal activity. *J Neurosci* 15, 623-642 (1995)

14. Steriade M: *Neuronal Substrates of Sleep and Epilepsy.* Cambridge University Press, Cambridge, UK (2003)

15. Steriade M & F. Amzica: Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Res Online* 1, 1-10 (1998)

16. Steriade M.: Impact of network activities on neuronal properties in corticothalamic systems. *J Neurophysiol* 86, 1-39 (2001)

17. Steriade M: *The Intact and Sliced Brain*. The MIT Press, Cambridge, MA (2001)

18. Hu B, M. Steriade & M. Deschênes: The effects of peribrachial stimulation on reticular thalamic neurons: the blockage of spindle waves. *Neuroscience* 31, 1-12 (1989)

19. Curró Dossi R, D. Paré & M. Steriade: Short-lasting nicotinic and long-lasting muscarinic depolarizing responses of thalamocortical neurons to stimulation of mesopontine cholinergic nuclei. *J Neurophysiol* 65, 393-406 (1991)

20. Steriade M: Corticothalamic resonance, states of vigilance and mentation. *Neuroscience* 101, 243-276 (2000)

21. Steriade M, R. Curró Dossi & A. Nuñez: Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortical potentiation and brainstem cholinergic suppression. *J Neurosci* 11, 3200-3217 (1991)

22. Gibbs F A & E. L. Gibbs: *Atlas of Electroencephalography* (2nd edition) Addison-Wesley, Cambridge (MA) (1952)

23. Steriade M, M. Deschênes, L. Domich & C. Mulle: Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol* 54, 1473-1497 (1985)

24. Steriade M, L. Domich, G. Oakson & M. Deschênes: The deafferented reticularis thalami nucleus generates spindle rhythmicity. *J Neurophysiol* 57, 260-273 (1987)

25. Wang X J & J. Rinzel: Spindle rhythmicity in the reticularis thalami nucleus: synchronization among mutually inhibitory neurons. *Neuroscience* 53, 899-904 (1993)

26. Destexhe A, D. Contreras, T. J. Sejnowski & M. Steriade: A model of spindle rhythmicity in the isolated thalamic reticular nucleus. *J Neurophysiol* 72, 803-818 (1994)

27. Golomb D, X. J. Wang & J. Rinzel: Synchronization properties of spindle oscillations in a thalamic reticular nucleus model. *J Neurophysiol* 72, 1109-1126 (1994)

28. Von Krosigk M, T. Bal & D. A. McCormick: Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261, 361-364 (1993)

29. Steriade M, D. A. McCormick & T. J. Sejnowski: Thalamocortical oscillation in the sleeping and aroused brain. *Science* 262, 679-685 (1993)

30. Contreras D, R. Curró Dossi & M. Steriade: Electrophysiological properties of cat reticular neurones *in vivo. J Physiol (Lond)* 470, 273-294 (1993)

31. Destexhe A, D. Contreras, M. Steriade, T. J. Sejnowski & J. R. Huguenard: *In vivo, in vitro* and computational analysis of dendritic calcium currents in thalamic reticular neurons. *J Neurosci* 16, 169-185 (1996)

32. Destexhe A, D. Contreras, T. J. Sejnowski & M. Steriade: Modeling the control of reticular thalamic oscillations by neuromodulators. *NeuroReport* 5, 2217-2220 (1994)

33. Contreras D, A. Destexhe, T. J. Sejnowski & M. Steriade: Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. *Science* 274, 771-774 (1996)

34. Contreras D, A. Destexhe, T. J. Sejnowski & M. Steriade: Spatiotemporal patterns of spindle oscillations in cortex and thalamus. *J Neurosci* 17, 1179-1196 (1997)

35. Kim U, T. Bal & D. A. McCormick: Spindle waves are propagating synchronized oscillations in the ferret LGNd *in vitro. J Neurophysiol* 74, 1301-1323 (1995)

36. Steriade M, P. Wyzinski & V. Apostol: Corticofugal projections governing rhythmic thalamic activity. In: *Corticothalamic Projections and Sensorimotor Activities*. Eds: Frigyesi T L, Rinvik E, Yahr M D, Raven Press, NY, 221-272 (1972)

37. Steriade M, M. Deschênes, P. Wyzinski & J. P. Hallé: Input-output organization of the motor cortex during sleep and waking. In: *Basic Sleep Mechanisms*. Eds: Petre-Quadens O, Schlag J, Academic Press, New York, 144-200 (1974)

38. Cisse Y, F. Grenier, I. Timofeev & M. Steriade: Electrophysiological properties and input-output organization of callosal neurons in cat association cortex. *J Neurophysiol* , in press (2003)

39. Contreras D & M. Steriade: Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. *J Neurosci* 15, 604-622 (1995)

40. Timofeev I. & M. Steriade: Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. *J Neurophysiol* 76, 4152-4168 (1996)

41. Amzica F & M. Steriade: The K-complex: its slow (<1 Hz) rhythmicity and relation to delta waves. *Neurology* 49, 952-959 (1997)

42. Timofeev I, M. Bazhenov, T. J. Sejnowski & M. Steriade: Contribution of intrinsic and synaptic factors in the desynchronization of thalamic oscillatory activity. *Thal & Rel Syst* 1, 53-69 (2001)

43. Bal T & D. A. McCormick: What stops synchronized thalamocortical oscillations? *Neuron* 17, 297-308 (1996)

44. Lüthi A & D. A. McCormick: Periodicity of thalamic synchronized oscillations: the role of Ca^{2+}- mediated upregulation of I_h. *Neuron* 20, 553-63 (1998)

45. Steriade M & M. Deschênes: Intrathalamic and brainstem-thalamic networks involved in resting and alert states. In: *Cellular Thalamic Mechanisms*. Eds: Bentivoglio M, Spreafico R, Elsevier, Amsterdam, 37-62 (1988)

46. Leresche N, D. Jassik-Gerschenfeld, M. Haby, I. Soltesz & V. Crunelli: Pacemaker-like and other types of spontaneous membrane potential oscillations of thalamocortical cells. *Neurosci Lett* 113, 72-77 (1990)

47. Leresche N, S. Lightowler, I. Soltesz, D. Jassik-Gerschenfeld & V. Crunelli: Low-frequency oscillatory

activities intrinsic to rat and cat thalamocortical cells. *J Physiol (Lond)* 441, 155-174 (1991)

48. McCormick D A & H. C. Pape: Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol (Lond)* 431, 291-318 (1990)

49. Curró Dossi R, A. Nuñez & M. Steriade: Electrophysiology of a slow (0.5-4 Hz) intrinsic oscillation of cat thalamocortical neurones *in vivo. J Physiol (Lond)* 447, 215-234 (1992)

50. Steriade M, A. Nuñez & F. Amzica: Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms. *J Neurosci* 13, 3266-3283 (1993)

51. Steriade M, D. Contreras & F. Amzica: Synchronized sleep oscillations and their paroxysmal developments. *Trends Neurosci* 17, 199-208 (1994)

52. Steriade M & R. W. McCarley: *Brainstem Control of Wakefulness and Sleep*. Plenum, New York (1990)

53. Uchida S, T. Maloney, J. D. March, R. Azari & I. Feinberg: Sigma (12-15 Hz) and delta (0.3-3.0) Hz EEG oscillate reciprocally within NREM sleep. *Brain Res Bull* 27, 93-96 (1991)

54. Lancel M, H. van Riezen & A. Glatt: The time course of σ activity and slow-wave activity during NREMS in cortical and thalamic EEG of the cat during baseline and after 12 hours of wakefulness. *Brain Res* 596, 285-295 (1992)

55. Dijk D J & C. A. Czeisler: Contribution of the circadian pacemaker and sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity. *J Neurosci* 15, 3526-3538 (1995)

56. Steriade M, S. Datta, D. Paré, G. Oakson & R. Curró Dossi: Neuronal activities in brainstem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J Neurosci* 10, 2541-2559 (1990)

57. Maquet P, D. Dive, E. Salmon, B. Sadzot, G. Franco, R. Poirrier & G. Franck: Cerebral glucose utilization during stage 2 sleep in man. *Brain Res* 571, 149-153 (1992)

58. Hofle N, T. Paus, D. Reutens, P. Fiset, J. Gotman, A. C. Evans & B. E. Jones: Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. *J Neurosci* 17, 4800-4808 (1997)

59. Villablanca J: Role of the thalamus in sleep control: sleep-wakefulness studies of chronic cats without the thalamus: the "athalamic cat". In: *Basic Sleep Mechanisms*. Eds: Petre-Quadens O, Schlag J, Academic Press, New York, 51-81 (1974)

60. Steriade M & G. Buzsáki: Parallel activation of thalamic and cortical neurons by brainstem and basal forebrain cholinergic systems. In: *Brain Cholinergic Systems*. Eds: Steriade M, Biesold D, Oxford University Press, Oxford, 3-63 (1990)

61. Schwindt P C, W. J. Spain, R. C. Foehring, C. E. Stafstrom, M. C. Chubb & W. E. Crill: Multiple potassium conductances and their functions in neurons from cat sensorimotor cortex *in vitro*. *J Neurophysiol* 59, 424-449 (1988)

62. Schwindt P C, W. J. Spain, R. C. Foehring, M. C. Chubb & W. E. Crill: Slow conductances in neurons from cat sensorimotor cortex *in vitro* and their role in slow excitability changes. *J Neurophysiol* 59, 450-467 (1988)

63. Steriade M, M. Deschênes & G. Oakson: Inhibitory processes and interneuronal apparatus in motor cortex during sleep and waking. I. Background firing and synaptic responsiveness of pyramidal tract neurons and interneurons. *J Neurophysiol* 37, 1065-1092 (1974)

64. Steriade M, A. Nuñez & F. Amzica: A novel slow (<1 Hz) oscillation of neocortical neurons *in vivo*: depolarizing and hyperpolarizing components. *J Neurosci* 13, 3252-3265 (1993)

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

66. Timofeev I, F. Grenier, M. Bazhenov, T. J. Sejnowski & M. Steriade: Origin of slow oscillations in deafferented cortical slabs. *Cerebr Cortex* 10, 1185-1199 (2000)

67. Sanchez-Vives M V & D. A. McCormick: Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat Neurosci* 3, 1027-1034 (2000)

68. Amzica F & M. Steriade: Disconnection of intracortical synaptic linkages disrupts synchronization of a slow oscillation. *J Neurosci* 15, 4658-4677 (1995)

69. Steriade M, I. Timofeev & F. Grenier: Natural waking and sleep states: a view from inside neocortical neurons. *J Neurophysiol* 85, 1969-1985 (2001)

70. Contreras D, I. Timofeev & M. Steriade: Mechanisms of long-lasting hyperpolarizations underlying slow sleep oscillations in cat corticothalamic networks. *J Physiol (Lond)* 494: 251-264 (1996)

71. Timofeev I, F. Grenier & M. Steriade: Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. *Proc Natl Acad Sci USA* 98, 1924-1929 (2001)

72. Steriade M, F. Amzica & A. Nuñez: Cholinergic and noradrenergic modulation of the slow (~0.3 Hz) oscillation in neocortical cells. *J Neurophysiol* 70, 1384-1400 (1993)

73. Krnjevic K, R. Pumain & L. Renaud: The mechanisms of excitation by acetylcholine in the cerebral cortex. *J Physiol (Lond)* 215, 247-268 (1971)

74. McCormick D A: Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Progr Neurobiol* 39, 337-388 (1992)

75. Massimini M & F. Amzica: Extracellular calcium fluctuations and intracellular potentials in the cortex during the slow sleep oscillation. *J Neurophysiol* 85, 1346-1350 (2001)

76. Amzica F & M. Steriade: Electrophysiological correlates of sleep delta waves. *Electroencephalogr Clin Neurophysiol* 107, 69-83 (1998)

77. Amzica F & M. Steriade: Neuronal and glial membrane potentials during sleep and paroxysmal oscillations in the cortex. *J Neurosci* 20, 6646-6665 (2000)

78. Wilson C J & Y. Kawaguchi: The origin of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J Neurosci* 16, 2397-2410 (1996)

79. Magill P J, P. Bolam & M. D. Bevan: Relationship of activity in the subthalamic nucleus - globus pallidus network to cortical EEG. *J Neurosci* 20, 820-833 (2000)

80. Mahon S, J. M. Deniau & S. Charpier: Relationship between EEG potentials and intracellular activity of striatal and cortico-striatal neurons: an *in vivo* study under different anesthetics. *Cerebr Cortex* 11, 360-373 (2001)

81. Tseng K Y, F. Kasanetz, L. Kargieman, L. A. Riquelne & M. G. Murer: Cortical slow oscillatory activity is reflected in the membrane potential and spike trains of striatal neurons in rats with chronic nigrostriatal lesions. *J Neurosci* 21, 6430-6439 (2001)

82. Steriade M, F. Amzica & D. Contreras: Synchronization of fast (30-40 Hz) spontaneous cortical rhythms during brain activation. *J Neurosci* 16, 392-417 (1996)

83. Steriade M, D. Contreras, F. Amzica & I. Timofeev: Synchronization of fast (30-40 Hz) spontaneous oscillations in intrathalamic and thalamocortical networks. *J Neurosci* 16, 2788-2808 (1996)

84. Grenier F, I. Timofeev & M. Steriade: Focal synchronization of ripples (80-200 Hz) in neocortex and their neuronal correlates. *J Neurophysiol* 86, 1884-1898 (2001)

85. Pavlov I P: "Innere Hemmung" der bedingten Reflexe und der Schlaf - ein und derselbe Prozess. *Skand Arch Physiol* 44, 42-58 (1923)

86. Eccles J C: Chairman's opening remarks. In: *The Nature of Sleep*. Eds: Wolstenholme G E W, O'Connor M, Churchill, London, 1-3 (1961)

87. Steriade M., D. Contreras, R. Curró Dossi & A. Nuñez: The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *J Neurosci* 13: 3284-3299 (1993)

88. Maquet P, C. Degueldre, G. Delfiore, J. Aerts, J. P. Péters, A. Luxen & G. Franck: Functional neuroanatomy of human slow wave sleep. *J Neurosci* 17, 2807-2812 (1997)

89. Morison R S & E. W. Dempsey: Mechanism of thalamocortical augmentation and repetition. *Amer J Physiol* 138, 297-308 (1942)

90. Castro-Alamancos M A & B. W. Connors: Spatiotemporal properties of short-term plasticity in sensorimotor thalamocortical pathways of the rat. *J Neurosci* 16, 2767-2779 (1996)

91. Castro-Alamancos M A & B. W. Connors: Cellular mechanisms of the augmenting response: short-term plasticity in a thalamocortical pathway. *J Neurosci* 16, 7742-7756 (1996)

92. Steriade M, I. Timofeev, F. Grenier & N. Dürmüller: Role of thalamic and cortical neurons in augmenting responses: dual intracellular recordings *in vivo. J Neurosci* 18, 6425-6443 (1998)

93. Timofeev I, F. Grenier, M. Bazhenov, A. Houweling, T. J. Sejnowski & M. Steriade: Cortical mechanisms of plasticity associated with augmenting responses and spindles. *J Physiol (Lond)* 542, 583-598 (2002)

94. Steriade M & I. Timofeev: Short-term plasticity during intrathalamic augmenting responses in decorticated cats. *J Neurosci* 17, 3778-3795 (1997)

95. Timofeev I & M. Steriade: Cellular mechanisms underlying intrathalamic augmenting responses of reticular and relay neurons. *J Neurophysiol* 79, 2716-2729 (1998)

96. Bazhenov M, I. Timofeev, M. Steriade & T. J. Sejnowski: Cellular and network models for intrathalamic augmenting responses during 10-Hz stimulation. *J Neurophysiol* 79, 2730-2748 (1998)

97. Bazhenov M, I. Timofeev, M. Steriade & T. J. Sejnowski: Computational models of thalamocortical augmenting responses. *J Neurosci* 18, 6444-6465 (1998)

98. Amzica F & M. Steriade: The functional significance of K-complexes. *Sleep Med Rev* 6, 139-149 (2002)

99. Steriade M, I. Timofeev, N. Dürmüller & F. Grenier: Dynamic properties of corticothalamic neurons and local cortical interneurons generating fast rhythmic (30-40 Hz) spike bursts. *J Neurophysiol* 79, 483-490 (1998)

100. Stickgold R, L. James & J. A. Hobson: Visual discrimination learning requires sleep after training. *Nat Neurosci* 3, 1237-1238 (2000)

101. Gais S, W. Plihal, U. Wagner & J. Born: Early sleep triggers memory for early visual discrimination skills. *Nat Neurosci* 3, 1335-1339 (2000)

102. Sejnowski T J & A. Destexhe: Why do we sleep? *Brain Res* 886, 208-223 (2000)

103. Khateb A, P. Fort, S. Williams, M. Serafin, B. E. Jones & M. Mühlethaler: Modulation of cholinergic nucleus basalis neurons by acetylcholine and *N*-methyl-*D*-aspartate. *Neuroscience*, 81, 47-55 (1997)

104. Rasmusson D D, J. C. Szerb & J. L. Jordan: Differential effects of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and N-methyl-D-aspartate receptor antagonists applied to the basal forebrain on cortical acetylcholine release and EEG desynchronization. *Neuroscience*, 72, 419-427 (1996)

105. Lavoie B & A. Parent: Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons. *J Comp Neurol*, 344, 190-209 (1994)

106. Steriade M, R. Curró Dossi, D. Paré & G. Oakson: Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc Natl Acad Sci USA* 88, 4396-4400 (1991)

107. Façon E, M. Steriade & N. Wertheimer: Hypersomnie prolongée engendrée par des lésions bilatérales du système activateur médial: le syndrome thrombotique de la bifurcation du tronc basilaire. *Rev Neurol (Paris)* 98, 117-133 (1958)

108. Paré D, Y. Smith, A. Parent & M. Steriade: Projections of upper brainstem cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* 25, 69-88 (1988)

109. Steriade M, D. Paré, A. Parent & Y. Smith: Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. *Neuroscience* 25, 47-67 (1988)

110. Glenn L L & M. Steriade: Discharge rate and excitability of cortically projecting intralaminar thalamic neurons during waking and sleep states. *J Neurosci* 2, 1287-1404 (1982)

111. Steriade M, D. Paré, S. Datta, G. Oakson & R. Curró Dossi: Different cellular types in mesopontine cholinergic nuclei related to ponto-geniculo-occipital waves. *J Neurosci* 10, 2560-2579 (1990)

112. Jones B E: Basic mechanisms of sleep-wake states. In: *Principles and Practice of Sleep Medicine*. Eds: Kryger M H, Toth T, Dement W C, Saunders, Philadelphia, 134-154 (2000)

113. Steriade M, G. Oakson & N. Ropert: Firing rates and patterns of midbrain reticular neurons during steady and transitional states of the sleep-waking cycle. *Exp Brain Res*, 46, 37-51 (1982)

114. Llinás R, A. A. Grace & Y. Yarom: *In vitro* neurons in mammalian cortical layer 4 exhibit intrinsic oscillatory activity in the 10- to 50-Hz frequency range. *Proc Natl Acad Sci USA* 88, 897-901 (1991)

115. Nuñez A, F. Amzica & M. Steriade: Voltage-dependent fast (20-40 Hz) oscillations in long-axoned neocortical neurons. *Neuroscience* 51, 7-10 (1992)

116. Gutfreund Y, Y. Yarom & I. Segev: Subthreshold oscillations and resonant frequency in guinea-pig cortical neurons: physiology and modelling. *J Physiol (Lond)* 483, 621-640 (1995)

117. Celesia G G & H. H. Jasper: Acetylcholine released from cerebral cortex in relation to state of activation. *Neurology* 16, 1053-1064 (1966)

Key Words: Sleep, Oscillations, Cortex, Thalamus, Intracellular, Review

Send correspondence to: Professor M. Steriade, M.D., D.Sc., Laboratory of Neurophysiology, School of Medicine, Laval University, Quebec, Canada G1K 7P4, Tel: 418-656-5547, Fax: 418-656-3236, E-mail: mircea.steriade@phs.ulaval.ca