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SLEEP AND AROUSAL: Thalamocortical Mechanisms

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ABSTRACT

Thalamocortical activity exhibits two distinct states: (*a*) synchronized rhythmic activity in the form of delta, spindle, and other slow waves during EEG-synchronized sleep and (*b*) tonic activity during waking and rapid-eye-movement sleep. Spindle waves are generated largely through a cyclical interaction between thalamocortical and thalamic reticular neurons involving both the intrinsic membrane properties of these cells and their anatomical interconnections. Specific alterations in the interactions between these cells can result in the generation of paroxysmal events resembling absence seizures in children. The release of several different neurotransmitters from the brain stem, hypothalamus, basal forebrain, and cerebral cortex results in a depolarization of thalamocortical and thalamic reticular neurons and an enhanced excitability in many cortical pyramidal cells, thereby suppressing the generation of sleep rhythms and promoting a state that is conducive to sensory processing and cognition.

INTRODUCTION

Even the first investigator to directly record the electrical activity in the mammalian cerebral cortex noted that the pattern of cortical activity was dependent upon the state of the animal (Caton 1887). Since this remarkable beginning, the investigation of the cellular correlates of sleep and arousal in thalamocortical systems has enjoyed several periods of rapid development. These include the demonstration of an ascending activating system in the brain stem that is essential for the generation of sleep-wake cycles (Bremer 1938, Moruzzi & Magoun

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1949, Jouvet 1962), and the proposal of hypotheses concerning the generation of sleep-related thalamocortical rhythms (reviewed in Andersen & Andersson 1968, Steriade & Deschênes 1984, Steriade et al 1993c). In the past 15 years, this base of information has been complemented by a dramatic increase in our knowledge of the mechanisms of the ionic, cellular, and network mechanisms through which thalamocortical activity is generated during sleep and of how this activity is disrupted in the transition to the waking state. In this review, we examine these more recent developments with a specific focus on the thalamus, a structure that is central to the generation of state-dependent activity in the forebrain.

During the periods of sleep that exhibit synchronization of the electroencephalogram (EEG-synchronized sleep), a number of rhythms are present. Two distinct rhythms that are particularly prominent in thalamocortical systems are delta waves and spindle waves (see Steriade & Deschênes 1984, Niedermeyer 1993). Delta waves in the normal adult are 0.5- to 4-Hz oscillations that are largest during deep sleep, while spindle waves appear as 1- to 3-s periods of waxing and waning 7- to 14-Hz oscillations that are superimposed upon the other rhythms of the EEG (see Figure 5, below). Researchers have known for some time that spindle waves are generated in the thalamus (reviewed in Steriade & Deschênes 1984), and these rhythms were the first for which a specific hypothesis of generation was proposed (Andersen & Andersson 1968).

Extracellular and intracellular recordings from thalamocortical neurons during EEG-synchronized sleep in naturally sleeping animals revealed that these cells generate repetitive burst discharges that ride on top of a slower depolarizing potential (Figure 1) (Hirsch et al 1983, McCarley et al 1983). The transition from EEG-synchronized sleep to the waking or REM-sleep states occurred with the progressive depolarization of thalamocortical cells and the abolition of the slow depolarizing spike and its associated burst of fast action potentials (Figure 1*B*). These alterations in the firing mode of thalamic neurons are associated with dramatic changes in the neurons' responsiveness to peripheral stimuli. For example, during EEG-synchronized sleep, there is a marked diminution of the responsiveness of LGNd thalamic neurons to activation of their receptive fields (Livingstone & Hubel 1981), presumably owing to the hyperpolarized state of these neurons, the interrupting effects of spontaneous thalamocortical rhythms, and the frequency limitations of the burst firing mode (see McCormick & Feeser 1990, Steriade & McCarley 1990). Over-powerful inhibition also may affect neuronal responsiveness during EEG-synchronized sleep; this inhibition is specifically reduced by activation of ascending cholinergic pathways (Ahlsen et al 1984, Francesconi et al 1988, McCormick & Pape 1988, Curró Dossi et al 1992b, Pape & McCormick 1995).

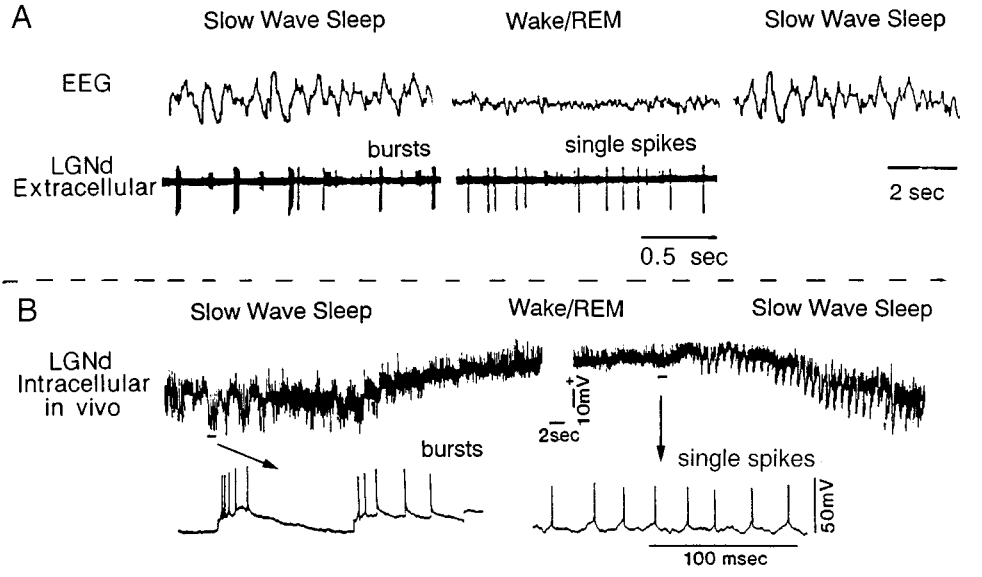


Figure 1 Lateral geniculate relay neurons display two distinct modes of action potential generation in relation to behavioral state and electroencephalogram (EEG). During periods of slow-wave sleep, the EEG exhibits synchronous slow waves, and LGNd relay neurons discharge in bursts of action potentials (*A*). In contrast, during waking or REM sleep, LGNd neurons fire in the single spike or tonic mode of action potential generation (*A*). Intracellular recordings in vivo during these transitions indicate that they are accomplished by depolarization of the membrane by 10–20 mV (*B*). (Part *A* from McCarley et al 1983. Part *B* from Hirsch et al 1983.)

These results, coupled with the earlier observations on the importance of the thalamus in the generation of sleep rhythms, suggest that the investigation of thalamic neurons and neuronal circuits may be particularly fruitful in the search to uncover the cellular mechanisms of sleep-wake alterations in the forebrain.

THALAMIC NEURONS EXHIBIT TWO STATES OF ACTIVITY

Early intracellular recordings of thalamocortical neurons in vivo revealed an unusual rebound burst discharge following hyperpolarization; this discharge could be generated by the intracellular injection of current or by the natural occurrence of an inhibitory postsynaptic potential (reviewed in Andersen & Andersson 1968, Deschênes et al 1984, Roy et al 1984). In vitro investigations revealed that the rebound potential occurring following hyperpolarization

is generated by activation of a specialized Ca^{2+} current, known as the low-threshold, or transient (I_T), Ca^{2+} current (Jahnsen & Llinás 1984a,b). Voltage-clamp analysis confirmed the presence of a large low-threshold Ca^{2+} current, as well as high-threshold Ca^{2+} currents, in thalamocortical cells (Coulter et al 1989, Crunelli et al 1989, Hernandez-Crus & Pape 1989). These investigations revealed that I_T shows both activation and inactivation. Activation occurs at membrane potentials positive to approximately −65 mV, while inactivation becomes complete, at steady state, at membrane potentials positive to approximately −65 mV. The kinetics of activation of I_T are considerably faster than are the kinetics of inactivation, similar to the Na^+ current underlying the generation of the more typical fast action potential. Therefore, if the membrane potential is depolarized from a relatively hyperpolarized membrane potential (negative to −65 mV), then I_T may first activate and then more slowly inactivate, generating a low-threshold Ca^{2+} spike (Figure 2*B*). These Ca^{2+} spikes typically last on the order of 100–200 ms, and in turn bring the membrane potential positive to threshold (approximately −55 mV) for the generation of a burst of three to eight fast action potentials (Figure 2*B*) (Jahnsen & Llinás 1984a,b).

Tonic depolarization of the membrane potential positive to approximately −65 mV results in the inactivation of I_T and therefore the suppression of burst discharges (e.g. Figure 2*A*). Following the inactivation of I_T, phasic depolarizations that bring the membrane potential positive to −55 mV, such as excitatory postsynaptic potentials, result in the generation of single, or trains of, action potentials; however, they do not generate high-frequency bursts (Jahnsen & Llinás 1984a,b, McCormick & Feeser 1990). Thus, the properties of I_T impart two distinct states of action potential generation onto thalamocortical cells: (*a*) burst firing upon removal of a hyperpolarization that surpasses −65 mV for a sufficient period of time and (*b*) tonic single-spike activity upon depolarization positive to approximately −55 mV.

Rhythmic Burst Firing and the Interaction of Two Ionic Currents

During EEG-synchronized sleep, thalamocortical cells generate rhythmic bursts of action potentials in the frequency range of 0.5–4 Hz, even during the generation of spindle waves, which occur at frequencies of 7–14 Hz (McCarley 1983, Roy et al 1984, Amzica & Steriade 1995a). Intracellular recordings in slices of cat LGNd maintained in vitro revealed a similar pattern of activity. Left unperturbed, a subpopulation of thalamocortical neurons generates low-threshold Ca^{2+} spikes in a rhythmic manner at a frequency of approximately 0.5–4 Hz (Figure 2) (McCormick & Pape 1990a, Leresche et al 1991, Soltesz et al 1991). This rhythmic burst firing results from the interaction of the low-threshold Ca^{2+} spike and a hyperpolarization-activated cation current known as

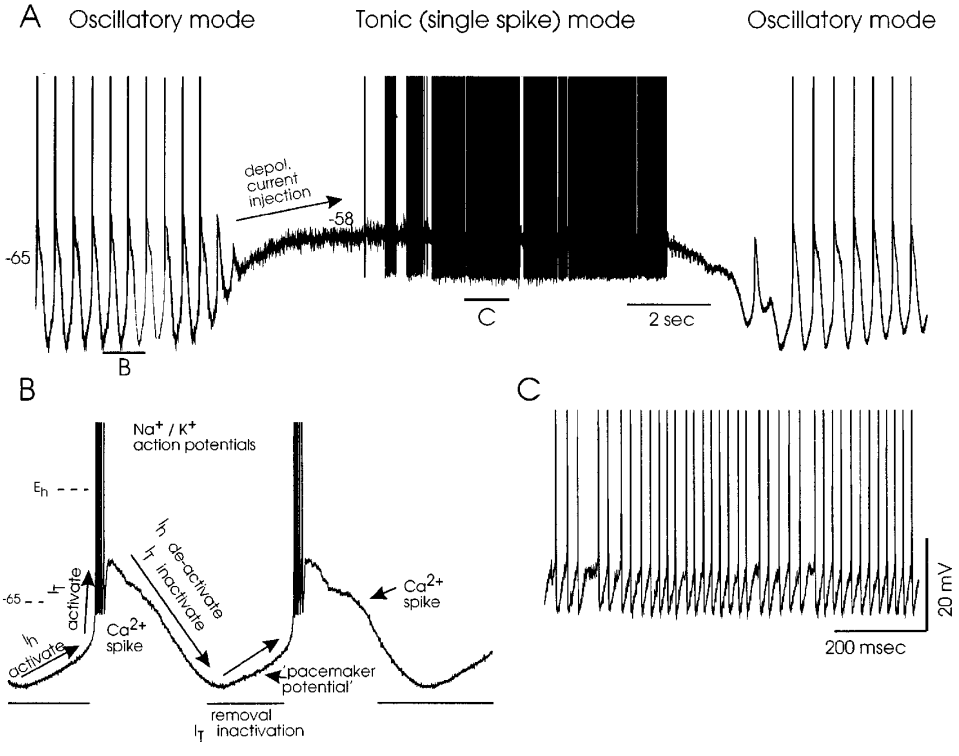


Figure 2 Thalamocortical neurons generate two distinct patterns of action potentials via the interaction of ionic currents. (*A*) This cat LGNd neuron generated rhythmic burst firing at a rate of about 2 Hz. Depolarization of the cell to −58 mV with the intracellular injection of current (*depol. current injection*) halted the rhythmic activity and switched the neuron to the tonic, or single spike, mode of action potential generation, owing to the inactivation of I_T. Removal of the depolarization reinstated the oscillatory activity. (*B*) Expanded trace of oscillatory activity and the proposed currents that largely mediate it. Activation of the low-threshold calcium current, I_T, depolarizes the membrane toward threshold for a burst of Na^+- and K^+-dependent fast action potentials. The depolarization deactivates the portion of I_h that was active immediately before the Ca^{2+} spike. Repolarization of the membrane due to I_T inactivation is followed by a hyperpolarizing overshoot, which is due to the reduced depolarizing effect of I_h. The hyperpolarization in turn de-inactivates I_T and activates I_h, which depolarizes the membrane toward threshold for another Ca^{2+} spike. (*C*) Expanded trace of single-spike activity. (From McCormick & Pape 1990a.)

the h-current (I_h). Hyperpolarization of thalamocortical neurons to membrane potentials negative to approximately −55 mV slowly activates a mixed Na^+ and K^+ current that depolarizes the neuron back toward the reversal potential of this current (approximately −35 mV). Consequently, the falling phase of a low-threshold Ca^{2+} spike is associated with the activation of I_h, and the activation of I_h results in a slow depolarization. This pacemaker potential again activates I_T and therefore another low-threshold Ca^{2+} spike.

The precise shape of the low-threshold Ca^{2+} spike may be controlled by the activation of a variety of K^+ currents that have been characterized in thalamocortical neurons (see Huguenard & McCormick 1992, Soltesz et al 1991, McCormick & Huguenard 1992). The interaction between the voltage dependence and the kinetics of the low-threshold Ca^{2+} current and the hyperpolarization-activated cation current result in the intrinsic propensity of thalamocortical neurons to generate rhythmic oscillations in the frequency range of 0.5–4 Hz (McCormick & Pape 1990a, McCormick & Huguenard 1992, Curró Dossi et al 1992a), which is the frequency range of delta waves. Computational models of single thalamocortical cells suggest that small shifts in the amplitude or voltage dependence of either I_T or I_h can result in large effects on the ability of single cells to generate rhythmic low-threshold Ca^{2+} spikes (McCormick & Huguenard 1992, Toth & Crunelli 1992, Destexhe et al 1993a,b). These findings are particularly relevant to the investigation of the mechanisms underlying the cessation of spindle waves and to the neurotransmitter control of synchronized thalamocortical rhythms (see below).

Thalamic Reticular Neurons also Exhibit Two States of Activity

Surrounding the thalamus and interposed between the thalamus and the cerebral cortex is a collection of GABAergic neurons known as the thalamic reticular nucleus (reviewed in Steriade & Deschênes 1984, Jones 1985). The perigeniculate nucleus is considered part of the thalamic reticular nucleus and is connected to the LGNd. The GABAergic neurons of the thalamic reticular and perigeniculate nuclei are innervated by axon collaterals of thalamocortical and corticothalamic neurons and give rise to a dense innervation of thalamocortical cells in a manner that often preserves reciprocal interactions between appropriate points in the thalamus, thalamic reticular nucleus, and cerebral cortex (see Steriade & Deschênes 1984, Jones 1985, Shosaku et al 1989, Uhlrich et al 1991, Bal et al 1995a,b, Pinault et al 1995a,b).

The GABAergic neurons of the thalamic reticular nucleus change their firing mode in a manner similar to that of thalamocortical cells (Steriade et al 1986). During periods of EEG-synchronized sleep, thalamic reticular cells generate

rhythmic high-frequency (350–450 Hz) bursts of action potentials, while during waking and REM sleep, these neurons generate sequences of tonic action potential activity. As in thalamocortical cells, these two activity states result from the properties of the low-threshold Ca^{2+} current (Figure 3) (Mulle et al 1986, Avanzini et al 1989, Huguenard & Prince 1992, Bal & McCormick 1993, Contreras et al 1993). However, these low-threshold Ca^{2+} spikes are distinct from those of thalamocortical neurons in an important way: Their voltage dependence is shifted to more positive membrane potentials (Huguenard & Prince 1992, Destexhe et al 1996) such that thalamic reticular cells can generate low-threshold Ca^{2+} spikes upon depolarization, even at membrane potentials of −65 mV. This particular property is important for the generation of synchronized thalamocortical rhythms, such as spindle waves, because the excitation of thalamic reticular neurons by thalamocortical and corticothalamic cells drives these rhythms (see below).

A pronounced after-hyperpolarization follows the generation of each low-threshold Ca^{2+} spike in thalamic reticular neurons as a result of an apamin-sensitive Ca^{2+}-activated K^+ conductance (I_{KCa}) (Avanzini et al 1989, Bal & McCormick 1993). This after-hyperpolarization by itself can be sufficient in amplitude and duration to remove enough inactivation of I_T in thalamic reticular neurons to result in the generation of an additional low-threshold Ca^{2+} spike (Figure 3*A1*). Through an interaction between I_T and I_{KCa}, therefore, these cells may generate rhythmic bursts of action potentials. The kinetics of I_T and I_{KCa} interact with the properties of thalamic reticular cells such that rhythmic firing occurs at frequencies of 0.5 to 12 Hz, depending upon the membrane potential of the cell (Avanzini et al 1989, Bal & McCormick 1993). Hyperpolarization of thalamic reticular neurons facilitates the occurrence and intensity of low-threshold Ca^{2+} spikes, but also reduces the frequency with which these neurons intrinsically oscillate (Bal & McCormick 1993).

Rhythmic burst firing in thalamic reticular neurons is often followed by a prolonged "tail" of single-spike activity in vivo and in vitro (Figure 3*A1*) (Domich et al 1986, Steriade et al 1986, Bal & McCormick 1993). This tonic tail of activity appears to be generated through the activation of a Ca^{2+}-activated nonselective cation current (I_{CAN}). Thus, thalamic reticular cells are endowed with the intrinsic propensity to generate (*a*) sequences of activity that take the form of burst-burst-burst-burst-tonic firing at relatively hyperpolarized membrane potentials (e.g. −65 mV or so) and (*b*) tonic, also known as single-spike, activity following depolarization to membrane potentials positive to approximately −55 mV (Figure 3), a state that can be imposed upon these cells through the actions of a variety of neuromodulatory transmitters (see below).

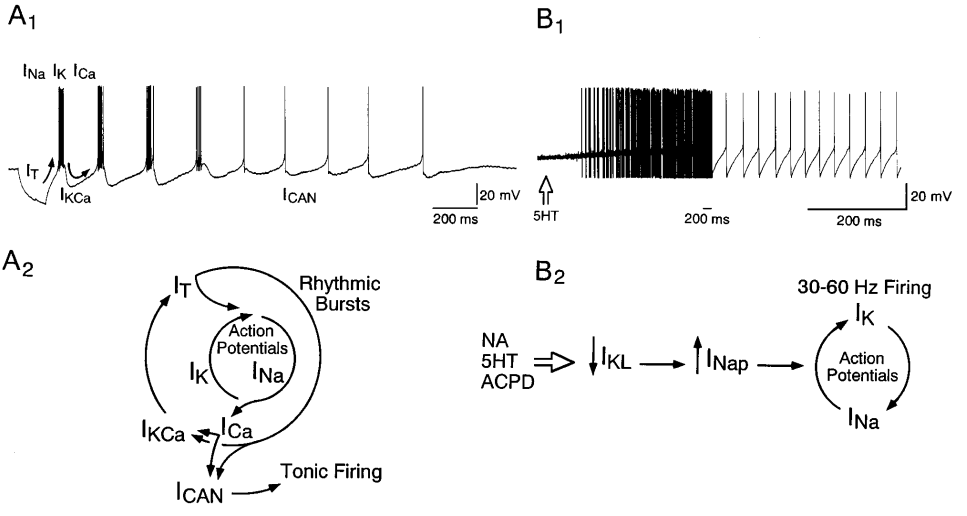


Figure 3 Idealized scheme of the ionic basis of rhythmic burst and tonic firing in thalamic reticular (perigeniculate) cells. Removal of a hyperpolarizing current pulse results in a low-threshold Ca^{2+} spike, which activates a high-frequency burst of action potentials mediated by the transient Na^+ current I_{Na} and various K^+ currents, collectively referred to as I_K. In addition, the fast Na^+ spikes also are likely to activate high-threshold Ca^{2+} currents, referred to here as I_{Ca}. The entry of Ca^{2+} results in the activation of Ca^{2+}-activated K^+ current and therefore an after-hyperpolarization. The depth and duration of this after-hyperpolarization determines the amplitude of the subsequent low-threshold Ca^{2+} spike, which is activated by the relaxation of the after-hyperpolarization. In addition to activating a Ca^{2+}-activated K^+ current, the entry of Ca^{2+} into the cell is also proposed to activate a Ca^{2+}-activated nonselective cation current (I_{CAN}) that results in a slow after-depolarization and the generation of tonic discharge at the end of the oscillatory burst firing (A_1, A_2). Activation of serotoninergic, noradrenergic, or glutamate metabotropic receptors results in a tonic depolarization of the cell, in part through the reduction of a resting "leak" potassium conductance (I_{KL}) that results in single-spike activity in the frequency range of 30–60 Hz. The frequency of this tonic activity may largely be determined by the interaction of the persistent Na^+ current (I_{Nap}) and the currents involved in action potential generation (B_1, B_2). (From Bal & McCormick 1993.)

SYNAPTIC INTERACTIONS BETWEEN THALAMOCORTICAL, THALAMIC RETICULAR, AND CORTICOTHALAMIC CELLS

Thalamic Reticular to Thalamocortical

Thalamocortical and thalamic reticular cells are highly interconnected in situ (Yen et al 1985, Cucchiaro et al 1991, Uhlrich et al 1991, Liu et al 1995, Pinault et al 1995a,b). Activation of the thalamic reticular and/or perigeniculate nuclei, either artificially or spontaneously through the generation of spindle waves

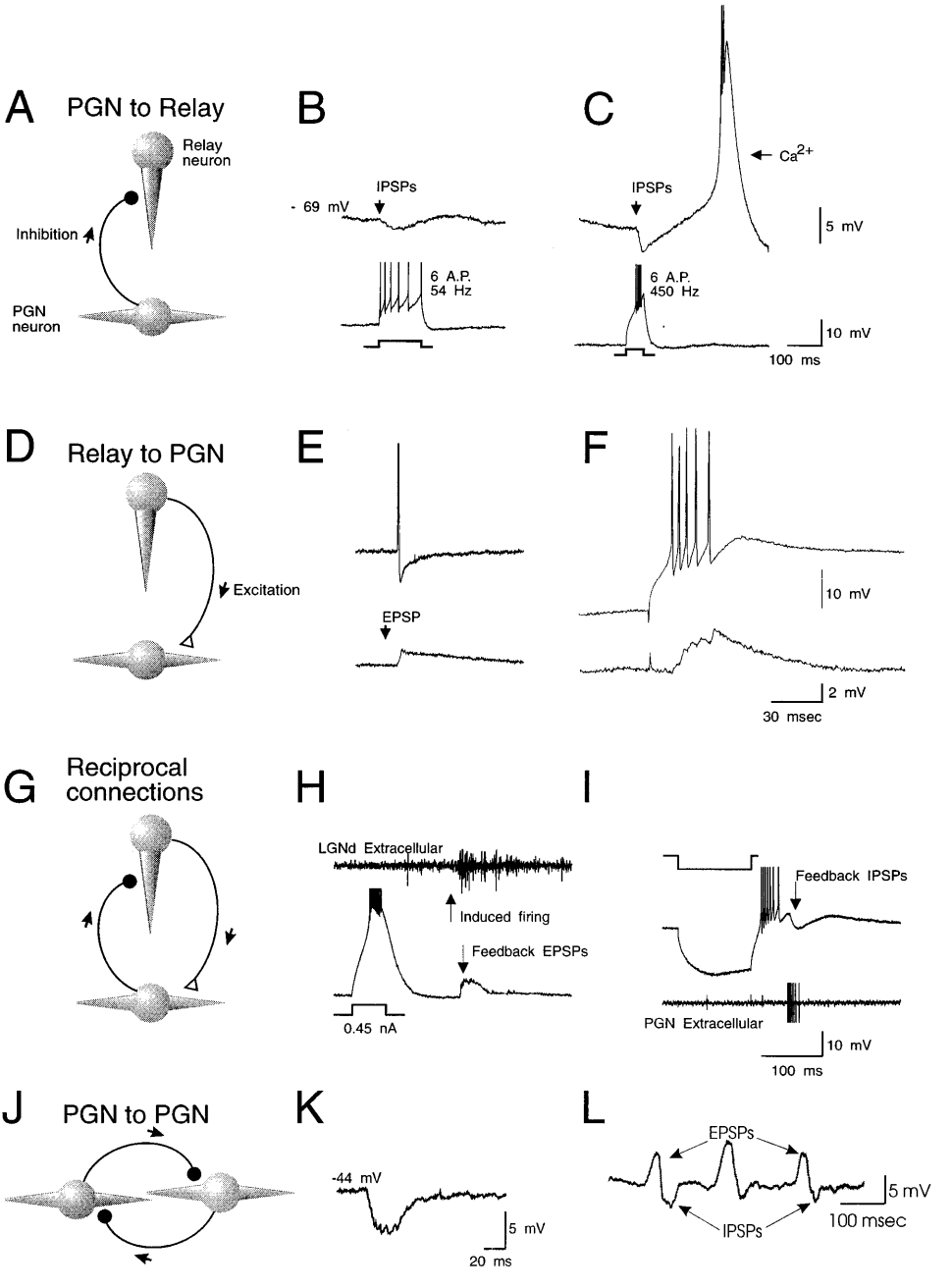
(see below), results in the generation of $GABA_A$ receptor–mediated inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons (Figure 4*A–C*) (Deschênes et al 1984, Thomson 1988, Huguenard & Prince 1994, Warren et al 1994, Bal et al 1995a,b, Sanchez-Vives et al 1995). These IPSPs can be sufficiently large in amplitude and long in duration to result in the generation of a rebound low-threshold Ca^{2+} spike, even if they are generated by only a single perigeniculate neuron (Figure 4*C*).

The activation of thalamic reticular neurons can also activate $GABA_B$ receptors in thalamocortical cells (Huguenard & Prince 1994, Bal et al 1995a,b, Sanchez-Vives et al 1995). The activation of $GABA_B$ receptors results, as it does in other central neurons, in the generation of slow inhibitory postsynaptic potentials through the activation of a G protein and an increase in a K^+ conductance (Crunelli et al 1988, McCormick 1991, Soltesz & Crunelli 1992). The long duration of $GABA_B$ receptor–mediated IPSPs facilitates the removal of inactivation of the low-threshold Ca^{2+} current; therefore these IPSPs can be followed by pronounced low-threshold Ca^{2+} spikes. Initial investigations suggest that in order to activate enough of a $GABA_B$-receptor IPSP in thalamocortical cells to be able to generate a rebound low-threshold Ca^{2+} spike, several thalamic reticular or perigeniculate cells must discharge simultaneously at a high rate (Sanchez-Vives et al 1995).

Thalamocortical to Thalamic Reticular

Activation of thalamocortical inputs to thalamic reticular and/or perigeniculate neurons results in the generation of excitatory postsynaptic potentials (EPSPs) through the activation of excitatory amino acid receptors (Figure 4*D–F*). Similarly, activation of corticothalamic fibers to thalamic reticular neurons also results in pronounced excitation, owing to the activation of excitatory amino acid receptors, and this excitation often results in the generation of rhythmic burst firing in these cells (De Curtis et al 1989, Bal & McCormick 1993, Contreras & Steriade 1996).

Bal et al (1995b) recently confirmed that thalamic reticular or perigeniculate neurons form disynaptic loops with thalamocortical cells in the ferret LGNd. Activation of a burst of action potentials with the intracellular injection of a current pulse into a single perigeniculate neuron typically results in the generation of a return barrage of EPSPs at a latency of approximately 100–150 ms (Figure 4*G* and *H*). These return EPSPs are generated through the rebound burst firing of thalamocortical neurons. Thus, the prolonged delay (100–150 ms) from the burst of action potentials in the perigeniculate cell and the return EPSPs is largely due to the duration of the $GABA_A$ receptor–mediated IPSP in the thalamocortical neuron (80–130 ms). A second cause for the delay is the time required for the generation of a Ca^{2+} spike to result in the


A
PGN to Relay
Relay neuron
Inhibition
PGN neuron
B
IPSPs
- 69 mV
6 A.P.
54 Hz
C
Ca2+
IPSPs
5 mV
6 A.P.
450 Hz
10 mV
100 ms
D
Relay to PGN
Excitation
E
EPSP
F
10 mV
2 mV
30 msec
G
Reciprocal connections
H
LGNd Extracellular
Induced firing
Feedback EPSPs
0.45 nA
I
Feedback IPSPs
PGN Extracellular
10 mV
100 ms
J
PGN to PGN
K
-44 mV
5 mV
20 ms
L
EPSPs
IPSPs
5 mV
100 msec

generation of a burst of action potentials (Bal et al 1995a). Surprisingly, the number of action potentials in the perigeniculate neuron that is required to generate rebound action potentials in a thalamocortical neuron can be remarkably small, with only two action potentials in a well-connected perigeniculate cell resulting in return EPSPs when the cells are at membrane potentials of around −65 mV.

The neurons of the thalamic reticular and perigeniculate nuclei innervate one another through local axonal collaterals, and perhaps in some species through dendrodendritic synapses (Ide 1982, Deschênes et al 1985, Uhlrich et al 1991), and inhibit one another through $GABA_A$, and possibly $GABA_B$, receptors (Figure 4*J* and *K*) (Ulrich & Huguenard 1995, Sanchez-Vives et al 1995). Intracellular recordings from perigeniculate neurons during the generation of spindle waves typically reveal barrages of EPSPs followed by, and overlapping with, barrages of IPSPs (Figure 4*L*) (Bal et al 1995b). Presumably these EPSP-IPSP barrages in the GABAergic neurons arise from the burst discharges of thalamocortical neurons followed by the induced burst discharges of neighboring perigeniculate cells (Bal et al 1995b). These $GABA_A$ receptor–mediated fast IPSPs strongly regulate the response of the perigeniculate neurons to the

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Figure 4 Synaptic interactions between thalamocortical and perigeniculate cells. (*A–C*) Activation of a perigeniculate neuron that monosynaptically innervates a thalamic relay cell results in inhibitory postsynaptic potentials (IPSPs). Generation of a tonic train of action potentials in the perigeniculate neuron through the intracellular injection of a current pulse results in a barrage of IPSPs in the thalamocortical cell but does not result in a rebound low-threshold Ca^{2+} spike. In contrast, activation of the perigeniculate neuron in the burst firing mode results in a larger IPSP and a rebound Ca^{2+} spike in the thalamocortical neuron. (*D–F*) Monosynaptic connections between thalamocortical and perigeniculate neurons. Generation of a single spike in the thalamocortical neuron results in a prolonged single excitatory postsynaptic potential (EPSP) in the perigeniculate cell. Generation of a burst of action potentials results in a barrage of EPSPs that exhibit temporal summation. (*G–I*) Pairs of perigeniculate and thalamocortical cells form reciprocal connections. Activation of a single perigeniculate cell (*H*) results in a rebound burst of action potentials in extracellularly recorded thalamocortical cells and a return barrage of EPSPs. A burst of action potentials in a single thalamocortical cell (*I*) results in a burst of action potentials in a perigeniculate cell and the generation of feedback IPSPs in the thalamocortical cell. (*J–K*) Perigeniculate neurons inhibit one another. Activation of perigeniculate neurons with the local application of glutamate results in the generation of IPSPs in a neighboring perigeniculate cell. (*L*) During the generation of spindle waves, perigeniculate cells receive barrages of EPSPs followed by IPSPs. Presumably the IPSPs are generated from the burst-firing of neighboring perigeniculate cells that are activated by the barrages of EPSPs from thalamocortical cells. (Parts *B, C,* and *H* from T Bal & DA McCormick, unpublished observations. Parts *E* and *F* from U Kim & DA McCormick, unpublished observations. Parts *I* and *L* from Bal et al 1995a. Part *K* from MV Sanchez-Vives & DA McCormick, unpublished observations.)

barrages of EPSPs. Block of $GABA_A$ receptors results in a large increase in the amplitude of the EPSP barrages and burst discharges of perigeniculate neurons (Bal et al 1995b, Sanchez-Vives et al 1995). Thus, the thalamic reticular and perigeniculate nuclei are envisioned to represent an interactive sheet of mutually inhibitory cells. The excitation of a particular point in these nuclei is expected to lead to the inhibition of neighboring GABAergic neurons. In the relay nuclei of the thalamus, this may appear as a central region of inhibition surrounded by an annulus of disinhibition.

Corticothalamic Inputs to Thalamocortical and Thalamic Reticular Neurons

Stimulation of the corticothalamic inputs to thalamocortical neurons results in monosynaptic EPSPs that involve both NMDA and non-NMDA receptors and in disynaptic IPSPs that involve intranuclear GABAergic interneurons and thalamic reticular cells (Deschênes & Hu 1990a, Scharfman et al 1990, von Krosigk & McCormick 1992). The monosynaptic EPSPs on thalamocortical neurons exhibit features that are consistent with the convergence of inputs from many layer-VI neurons onto single thalamocortical cells; they also exhibit marked frequency-dependent facilitation (e.g. see Deschênes & Hu 1990a). Corticothalamic cells in layer VI may be contacted with thalamocortical afferents, and therefore only a one-synapse loop may separate the thalamus and the cerebral cortex (White & Hersch 1982). Repetitive stimulation of corticothalamic fibers activates not only the fast ionotropic receptor–mediated EPSPs in thalamocortical neurons, but also a slow, long-lasting (up to one minute duration) EPSP that is generated through a reduction in a leak K^+ conductance and that may be mediated through the activation of glutamate metabotropic receptors (McCormick & von Krosigk 1992). These properties are in marked contrast to prethalamic inputs, such as those from the retina, which typically do not exhibit frequency-dependent facilitation or the generation of slow EPSPs (see McCormick & von Krosigk 1992; reviewed in McCormick 1992).

Thalamocortical and Thalamic Reticular Cells Interact to Generate Spindle Waves

The capability of a burst of action potentials in a thalamic reticular or perigeniculate neuron to generate a rebound low-threshold Ca^{2+} spike and a burst of action potentials in thalamocortical neurons, which then returns to the same thalamic reticular cell as a barrage of EPSPs, is the proposed basis of spindle wave generation (von Krosigk et al 1993, Bal et al 1995a,b; see also Steriade & Deschênes 1984, Buzsáki et al 1990, Steriade et al 1993c). The intracellular recordings of spindle waves in vivo by Andersen & Andersson (1968) revealed

that during these oscillations, thalamocortical cells receive repetitive IPSPs at the frequencies of spindle wave generation, namely 7–14 Hz. Some of these IPSPs were associated with the rebound generation of bursts of action potentials, which these authors proposed had excited the GABAergic neurons responsible for the generation of the IPSPs in the first place. Andersen & Andersson (1968) envisioned that spindle waves were generated through a circuitous interaction between the excitatory thalamocortical cells and inhibitory intrathalamic GABAergic neurons. The location of these GABAergic neurons was proposed to be local, within each thalamic nucleus (Andersen & Andersson 1968). More recent investigations by Steriade, Deschênes, and colleagues, however, have demonstrated that the GABAergic neurons responsible for spindle wave generation are located in the thalamic reticular nucleus (Steriade et al 1985, 1987). Surgical isolation of the thalamic reticular nucleus from the rest of the thalamus abolishes spindle waves in thalamocortical neurons but preserves synchronized spindle-like oscillations in the thalamic reticular nucleus. These findings led Steriade et al (1987) to propose that the thalamic reticular nucleus acts as a pacemaker in the generation of spindle waves. One proposed mechanism was that thalamic reticular neurons may interact with one another through dendrodendritic and axonal connections to generate and synchronize spindle waves (Deschênes et al 1985, Steriade et al 1987).

Contrary to this suggestion, intracellular recordings from thalamic reticular neurons have not revealed the occurrence of rebound burst discharges in response to IPSPs, as would be expected if spindle waves were generated through the interaction with other thalamic reticular neurons. Instead, these recordings have consistently revealed that each burst of action potentials in thalamic reticular cells is generated by a low-threshold Ca^{2+} spike that itself is triggered by the arrival of a barrage of EPSPs (Mulle et al 1986, Shosaku et al 1989, Steriade et al 1993b, Contreras & Steriade 1995). These barrages of EPSPs often occur as clusters of three to five individual events that have the identical frequency components associated with burst firing in thalamocortical neurons, suggesting that they originate in thalamocortical neurons (Mulle et al 1986).

The discovery of a slice preparation that spontaneously generated spindle waves allowed for the detailed analysis of the neuronal circuitry involved in the generation of this synchronized rhythm (von Krosigk et al 1993). Intracellular recordings in vitro from thalamocortical neurons of the ferret LGNd revealed barrages of IPSPs arriving at approximately 6–10 Hz (Figure 5). These spindle wave–associated IPSPs are remarkably similar to those recorded in vivo (Andersen & Andersson 1968, Steriade & Deschênes 1984). Spindle wave IPSPs in the ferret LGNd are generated through the activation of $GABA_A$ receptor–mediated increases in Cl^- conductance and arise from the burst firing

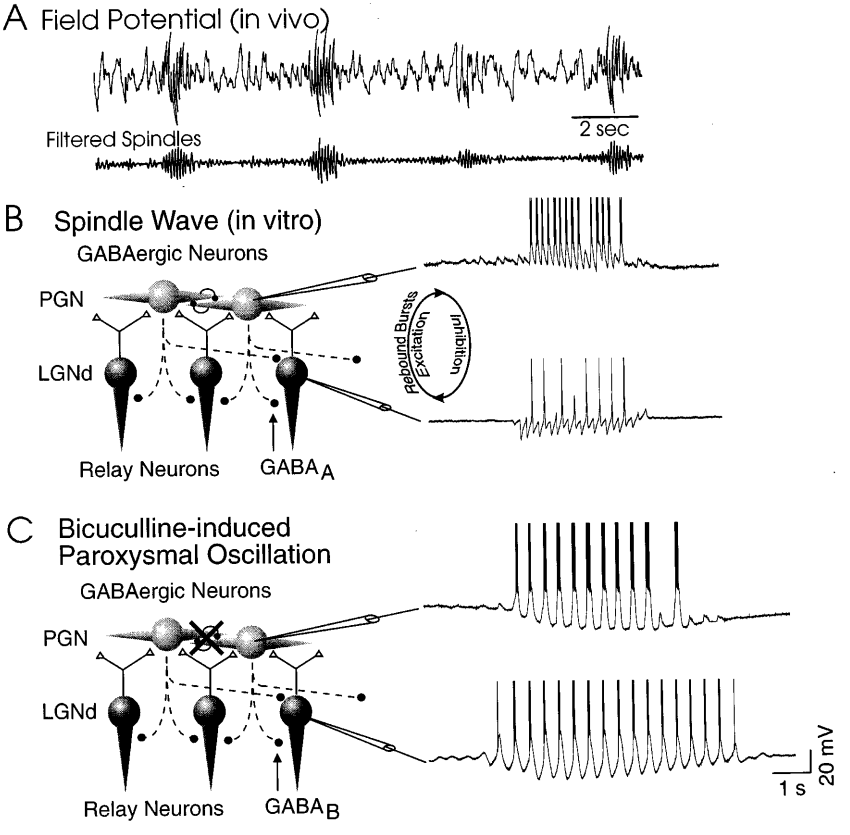


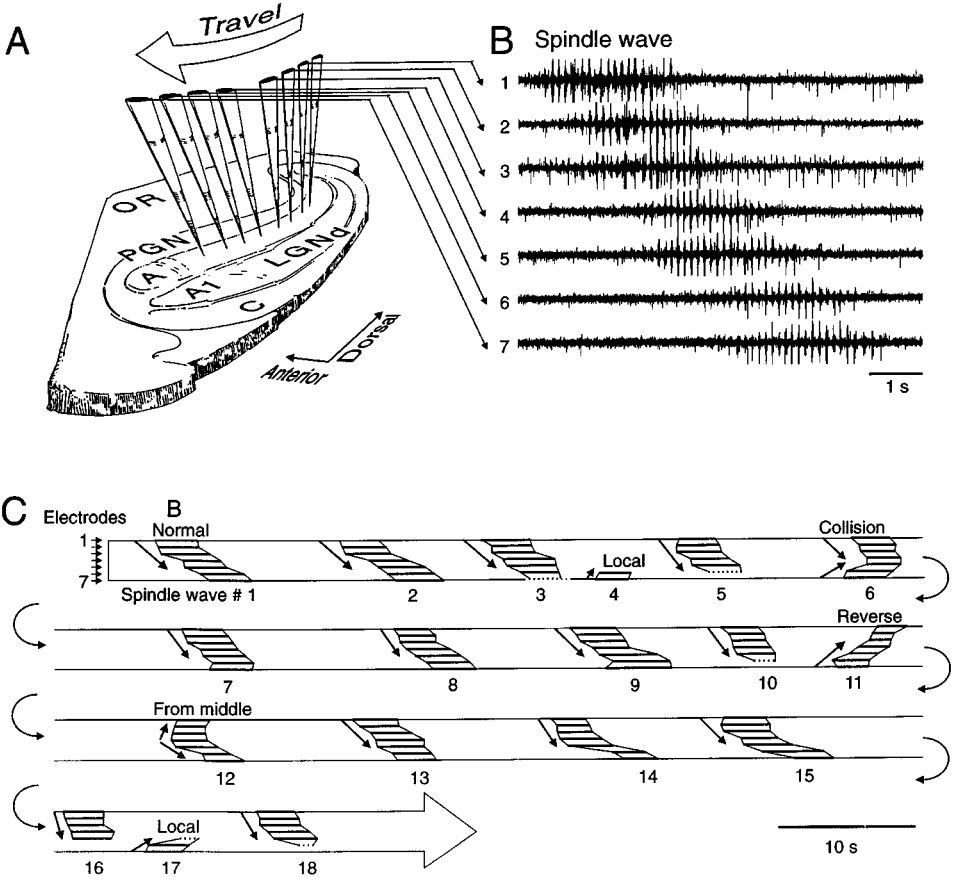
Figure 5 Spindle waves and the interaction between thalamic reticular or perigeniculate cells and thalamocortical cells during spindle wave generation. (*A*) Field potential recording in cat intralaminar central lateral thalamic nucleus. Filtering of the field potential recording reveals spindle waves. (*B*) Spindle waves are generated in vitro by an interaction between perigeniculate neurons and relay neurons such that perigeniculate neurons inhibit a number of relay neurons, some of which rebound burst following each IPSP. These rebound bursts activate low-threshold Ca^{2+} spikes and action potential bursts in perigeniculate neurons. During the spindle wave, perigeniculate neurons progressively hyperpolarize, which increases and then decreases their participation in spindle wave generation. (*C*) Blocking $GABA_A$ receptors results in the disinhibition of perigeniculate neurons from one another. It also increases the intensity of action potential bursts in perigeniculate neurons, increases the activation of $GABA_B$ receptors on relay cells, and subsequently increases the bursts of action potentials in relay neurons. This increase in relay neuron discharge also increases the activation of perigeniculate neurons. Thus blocking $GABA_A$ receptors results in the generation of a slowed paroxysmal discharge that is critically dependent upon $GABA_B$ receptors for its generation. (Part *A* from Steriade & Llinás 1988. Parts *B* and *C* from Bal et al 1995a.)

of nearby perigeniculate neurons (Bal et al 1995a,b). Thalamocortical neurons generate rebound low-threshold Ca^{2+} spikes following only a subset of IPSPs at a frequency of approximately 2–4 Hz (Bal et al 1995a,b), as has been observed in vivo (Deschênes et al 1984, Roy et al 1984). When thalamocortical neurons do burst, they are in marked synchrony with neighboring thalamocortical cells (Bal et al 1995a,b, Kim et al 1995). This frequency transformation property of thalamocortical cells is explained by their intrinsic propensity to rhythmically burst at 2–4 Hz, owing to the interaction of I_T and I_h (Bal et al 1995a, Wang 1994).

Intracellular recordings from perigeniculate neurons revealed repetitive burst discharges during the generation of spindle waves. These repetitive burst discharges typically occur in the frequency range of 0.5–12 Hz, which is a higher frequency than that seen in thalamocortical cells. Close inspection of the perigeniculate burst discharges during spindle wave generation revealed that each is associated with the generation of a low-threshold Ca^{2+} spike that itself is activated by a large barrage of EPSPs that result from burst firing in thalamocortical cells (Figure 5). Thus, spindle waves in the ferret LGNd in vitro result from the interaction of thalamocortical and perigeniculate cells in a manner that is predicted by their disynaptic connections: The activation of a burst discharge in a thalamic reticular or perigeniculate neuron results in the generation of an IPSP in a thalamocortical cell. This IPSP removes inactivation of the low-threshold Ca^{2+} current, and the repolarizing phase of the IPSP activates this current, giving rise to a low-threshold Ca^{2+} spike and a burst of action potentials. It is this burst of action potentials in thalamocortical cells that subsequently activates once again the perigeniculate neurons. The time required for one completion of this loop between thalamocortical cells and thalamic reticular neurons explains the frequency range of spindle waves (6–10 Hz in ferrets).

In the intact animal, burst discharges in thalamocortical cells communicate spindle waves to the cerebral cortex. Cortical pyramidal cells respond to the arrival of these barrages of EPSPs with the occasional generation of action potentials (Andersen & Andersson 1968, Contreras & Steriade 1996). The occurrence of such action potentials in identified corticothalamic neurons, as well as the potent excitatory influence of corticothalamic fibers on thalamic reticular and thalamocortical neurons, suggests that corticothalamic cells may also participate in the generation of spindle waves. The simultaneous recording of cortical, thalamic reticular, and/or thalamocortical neurons and field potentials reveals phase relations that are consistent with the hypothesis that both the cortical and thalamic reticular neurons are being driven by activity in thalamocortical cells (Contreras & Steriade 1996).

SPINDLE WAVES CAN PROPAGATE The simultaneous recording from eight sites in the ferret LGNd in vitro revealed that spindle oscillations propagate across the slice at a rate of approximately 1 mm/s, or about 100 μm per burst of activity (Figure 6) (Kim et al 1995). This propagation typically occurs in the dorsal-ventral plane of sagittal slices, starting at one end of the slice and propagating in a somewhat saltatory manner to the other. The propagation occurs simultaneously in the perigeniculate nucleus and in all laminae of the LGNd along the lines of projection of connections between these two structures. The local pharmacological block of excitatory inputs from thalamocortical cells to the perigeniculate nucleus prevents spindle waves from propagating past the point of application. The areas of the tissue dorsal and ventral to the block



generate spindle waves independently. On occasion, two different regions of a normal slice may generate spindle waves that then propagate toward each other. As long as the two spindle waves do not share the same region of the slice, they act as independent oscillators. However, once the oscillations propagate to the same portion of the LGNd and perigeniculate nucleus, they become synchronized into one spindle wave (Kim et al 1995). Spindle wave generation and propagation exhibit a refractory period of approximately 3–20 s. Owing to this refractory period, colliding spindle waves do not pass one another.

Activation of even a single well-connected perigeniculate neuron can result in the generation and propagation of a spindle wave throughout the LGNd slice if the perigeniculate cell is activated near the end of the refractory period. If this neuron is in the middle of the dorsal-ventral extent of the slice, then the spindle wave propagates in a V-like pattern away from the activated perigeniculate cell. Based upon these observations, researchers have proposed that the propagation of spindle waves in vitro occurs as a result of a zig-zag interaction between thalamocortical cells in the LGNd and the GABAergic neurons of the perigeniculate nucleus such that each disynaptic loop of activity between these

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Figure 6 Spindle waves are propagating network oscillations in the ferret geniculate slice. (*A*) Drawing of a sagittal ferret LGNd slice with an array of eight multiunit electrodes arranged in lamina A along the dorsal-ventral (D-V) axis. The electrodes are regularly spaced about 250–400 μm apart, extending approximately 2–3 mm in the D-V axis. (*B*) Example of a recording of a spindle wave propagating through an array of seven electrodes. The spindle wave starts at the dorsal end of the slice and propagates ventrally. Each spindle wave waxed and waned over 2–3 s and consisted of rhythmic action potential bursts with interburst frequencies of 6–10 Hz. (*C*) Schematic diagram of propagation of 18 consecutive spindle waves. The duration of spindle oscillation at each recording site shown in *A* is plotted as a horizontal thick bar, while the start and stop of spindles at adjacent recording sites are connected with thin lines. The arrows indicate the direction of spindle wave propagation. Spindle oscillations normally propagated from dorsal (*electrode 1*) to ventral (*electrode 7*) at a speed of 0.4–0.8 mm/s. Neurons at the ventral end of the slice (*recording sites 6, 7*) generated spindle waves in a semi-independent fashion. Spindle waves that started from the dorsal end sometimes did not invade these areas (*spindles 3, 5, 10, 16, 18*) or did so with a delay (*spindles 14, 15*). Neurons at the ventral end (*recording sites 6, 7*) could also initiate spindle oscillations and generated local (*spindles 4, 17*) or reverse (*spindle 11*) propagation of spindle waves. When the spindle oscillations were initiated simultaneously from both dorsal and ventral ends, the two spindle waves propagated in opposite directions and collided in the middle (*spindle 6*). The local propagation of spindle waves and the stoppage of spindle propagation at the point of collision both indicate the presence of a refractory period for spindle wave generation and propagation. Dashed line segments represent periods of only weak activity in the extracellular recordings. The four segments in *C* are continuous in time, as indicated by the curved arrows. (From Kim et al 1995.)

two cell groups is associated with the recruitment of neurons into the network oscillation at the edge or front of the activity. However, as the spindle wave generalizes, the network also starts to become refractory, such that the spindle wave ends after approximately 1–3 s. First, it ends at the site of initiation; then, this waning of the spindle wave propagates through the tissue, as did the growth, or waxing, of the spindle wave (Kim et al 1995).

Previous multiple-site extracellular recordings in vivo have revealed the presence of two types of spindle waves: one that propagates in a manner similar to that observed in vitro, and one in which propagation is less clear (reviewed in Andersen & Andersson 1968). In this second type of spindle wave, the network oscillations occur in widely dispersed regions of the cerebral cortex at approximately the same time. More recent simultaneous recordings of spindle waves in anesthetized or sleeping cats suggest that this second type of spindle wave is by far the most prevalent, although spindle waves that slowly propagate can also occur, particularly in response to local cortical stimulation (D Contreras, A Destexhe & M Steriade, unpublished observations). The cellular mechanisms by which spindle waves may be generated throughout wide portions of the cerebral cortex and thalamus in near simultaneity, indicating rapid propagation throughout the thalamocortical system, are not yet known. The widespread axonal arbors of a subset of thalamic reticular, thalamocortical, corticothalamic, and corticocortical connections are likely involved (see Steriade et al 1984, Jones 1985, Felleman & Van Essen 1991). We propose that the synchronization of spindle waves is largely the result of divergence and convergence of axonal connections between interacting neuronal groups (see Kim et al 1995).

MECHANISMS OF GENERATION OF THE SPINDLE WAVE REFRACTORY PERIOD

The mechanisms of the generalization of synchronized oscillations, such as the waxing of spindle waves, appear to be relatively clear: The presence of axonal connections between the interacting cells recruits additional cells into the network oscillation. However, the mechanisms by which spindle waves spontaneously stop have been less clear. Previous explanations have centered on the desynchronization of the network (Andersen & Andersson 1968, Contreras & Steriade 1996) and the depolarization or hyperpolarization of thalamic reticular neurons (Domich et al 1986; von Krosigk et al 1993).

Recent investigations in the ferret LGNd in vitro have revealed that events in thalamocortical cells may explain the waning of spindle waves. Intracellular recordings demonstrate that the refractory period for spindle wave generation is associated with a prolonged after-depolarization and an increase in membrane conductance. Both of these can be activated with an intracellular injection of repetitive hyperpolarizing current pulses that mimic the arrival of spindle wave

IPSPs. This result indicates that the after-depolarization is generated as an intrinsic property of thalamocortical neurons (Bal & McCormick 1995, 1996), as was observed previously in spontaneously oscillating thalamocortical neurons (Leresche et al 1991, Soltesz et al 1991). The spindle wave–associated after-depolarization results in a marked reduction in the ability of thalamocortical cells to generate rebound low-threshold Ca^{2+} spikes following the arrival of IPSPs from perigeniculate neurons. This reduced ability to generate rebound Ca^{2+} spikes presumably results from the voltage-dependent inactivation of I_T. An analysis of the properties of the after-depolarization suggests that it may be mediated by a persistent activation of the hyperpolarization-activated cation conductance I_h. Indeed, the after-depolarization, increase in membrane conductance, and spindle wave refractory period are all selectively blocked by the extracellular application of Cs^+, a known blocker of the h-current. Based upon these findings, we have suggested that spindle waves may wax and wane during the progressive recruitment of more and more neurons into the oscillation through axonal collaterals, while at the same time, the h-current may become more and more activated, resulting in a depolarization of thalamocortical cells and a progressive reduction in their ability to generate rebound burst discharges, ultimately resulting in the cessation of this network activity. The spindle wave refractory period (3–20 s) is the time required for the h-current to return to a level that allows another spindle wave to occur (Bal & McCormick 1995, 1996; see also Soltesz et al 1991). What could cause the persistent activation of the h-current during the generation of a spindle wave? Two possibilities are that the voltage dependence of the h-current is shifted to more positive levels by increases in the intracellular Ca^{2+} concentration, or that the h-current exhibits slow deactivation kinetics at normal resting membrane potentials (see Hagiwara & Irisawa 1989, Destexhe et al 1993a,b).

Delta and Spindle Waves May Be Grouped by a Slow Corticothalamic Oscillation

In the naturally sleeping or anesthetized cat, delta and spindle waves do not occur continuously but rather can recur on a regular basis in groups every 2–10 s (Steriade et al 1993b,d,e). Simultaneous recordings of cortical, thalamocortical, and thalamic reticular neurons reveal that this slow rhythm is associated with a relatively synchronized hyperpolarization followed by the sudden depolarization of all cell types (including local interneurons in the cerebral cortex) (Figure 7) (Steriade et al 1993a,b,d,e, Amzica & Steriade1995a,b, Contreras & Steriade 1995). The depolarization in cortical cells consists of a mixture of EPSPs and IPSPs, while the hyperpolarization appears to be a cessation of these synaptic barrages. Cortical-cortical interconnections are critically important in the generation and synchronization of this slow oscillation, since

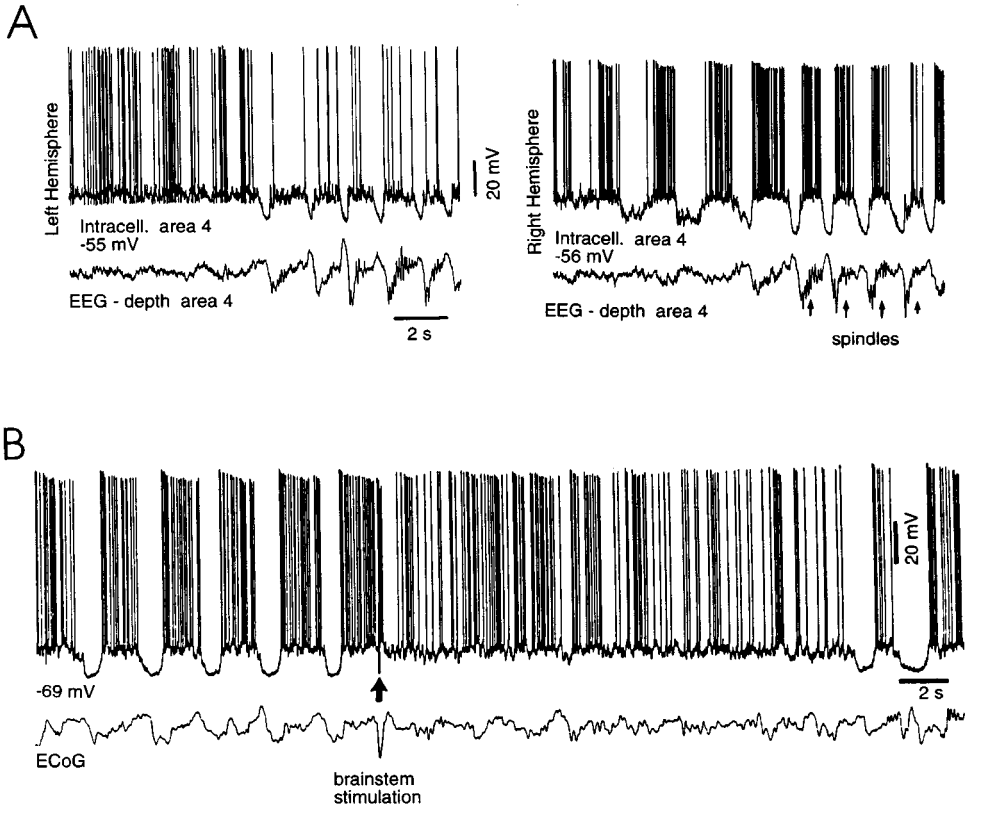

Figure 7 The slow (<1 Hz) rhythm of cortical neurons and suppression with brain stem stimulation. (*A*) Simultaneous intracellular recordings from two neurons, from left and right precruciate areas 4, together with depth EEG from the same areas. Note the development from nonoscillatory to oscillatory state. Spindle oscillations are generated in synchrony with the slow rhythm. (*B*) Block of the slow oscillation by stimulation (5 shocks at 100 Hz) (*arrow*) of the pedunculopontine tegmental nucleus. Recordings are from area 5. Data were recorded from cats anesthetized with ketamine and xylazine. (Part *A* from Steriade et al 1994. Part *B* from Steriade et al 1993a.)

it survives massive lesions of the appropriate nuclei of the thalamus (Steriade et al 1993b,d,e), and synchronization is disrupted with block of intracortical connections (Amzica & Steriade 1995b).

In the intact brain, cortical and thalamic networks interact extensively during the generation of the sleep EEG, resulting in a coordinated occurrence of corticothalamocortical rhythms. For example, the initial portion of the depolarization associated with the slow oscillation can trigger thalamic circuits to

generate a spindle wave (Figure 7) (Steriade et al 1993b, Contreras & Steriade 1995), resulting in a pattern similar to the K-complex of EEG-synchronized sleep (see Niedermeyer 1993). The slow oscillation may also be associated with the activation of groups of delta (0.5–4 Hz) oscillations in cortical networks (Steriade et al 1993b,e), although the precise cellular mechanisms for the generation of delta oscillations are still unknown (see Steriade 1993). Stimulation of the brain stem results in an abolition of the slow (<1 Hz) rhythm, an abolition of spindle waves and delta waves, and a promotion of higher frequency (20–60 Hz) activity (Steriade et al 1993a). Electrical stimulation in the region of the pedunculopontine nucleus, which is cholinergic, results in a muscarinic receptor–mediated suppression of the rhythmic hyperpolarization of the slow oscillation. During this activation, the cortical neurons remain in the depolarized state. Similarly, repetitive stimulation of the locus coeruleus, which is noradrenergic, can also result in the suppression of the slow rhythm through a suppression of the hyperpolarizing lulls between the depolarizing sequences (Steriade et al 1993a).

Together, these results suggest that the depolarized state is generated by the reentrant excitation of cortical networks through corticocortical as well as corticothalamocortical synaptic connections. These reverberating excitatory circuits are tempered during the depolarized state by the activation of local inhibitory networks within the cortex and thalamus. The activation of components of the ascending activating system results in a suppression of the various slow thalamocortical rhythms, presumably through a depolarization of thalamic neurons and an increase in neuronal excitability in cortical networks (reviewed in Steriade & McCarley 1990, McCormick 1992).

Perversion of Spindle Waves into Paroxysmal Events

Absence epileptic seizures are characterized by a remarkable 3-Hz synchronized spike-and-wave oscillation in thalamocortical networks that consists of pronounced burst discharges during the spike interspersed with inhibition during the wave (reviewed in Avoli et al 1990, Steriade et al 1994). The cellular mechanisms for generation of absence seizures appear to be related to those for the generation of normal thalamocortical rhythms during sleep. Many children that exhibit this form of epilepsy have the majority of their seizures during EEG-synchronized sleep (Kellaway 1985), and at least some animal models of absence, or spike-and-wave, seizures have revealed a strong relationship between the mechanisms for the generation of spindle waves and the generation of spike-and-wave seizures (Avoli et al 1990, Buzsáki et al 1990). Recent investigations in rodent models reveal two key points: Activation of the thalamic reticular nucleus is essential (Buzsáki et al 1988) and activation of $GABA_B$ receptors in thalamic relay nuclei is important (Hosford et al 1992, Liu et al

1992, Snead 1992) for the generation of spike-and-wave seizures. Because activation of $GABA_B$ receptors on thalamocortical neurons is particularly efficient in causing rebound burst discharges in these neurons (Crunelli & Leresche 1991) and because activation of the thalamic reticular nucleus can result in the activation of $GABA_B$ receptors in thalamocortical neurons, one might suspect that a circuitous interaction between the thalamic reticular nucleus and thalamocortical cells may be involved in the generation of these paroxysmal events (Buzsáki et al 1990).

The pharmacological block of $GABA_A$ receptors in ferret geniculate slices results in the transformation of spindle waves into paroxysmal activity such that both thalamocortical and perigeniculate neurons greatly increase the intensity of their burst discharges and become phase-locked into a 2- to 4-Hz rhythm (Figure 5) (von Krosigk et al 1993, Bal et al 1995a,b). Bal et al (1995a,b) suggested that this shift from normal to paroxysmal activity resulted from the disinhibition of perigeniculate neurons from one another, resulting in an increase in discharge of these cells and a large increase in the postsynaptic activation of $GABA_B$ receptors in thalamocortical neurons (see Huguenard & Prince 1994, Sanchez-Vives et al 1995). The long duration of $GABA_B$ receptor–mediated IPSPs enhances the removal of inactivation of I_T, thereby resulting in large rebound bursts of action potentials, which excite the perigeniculate neurons even more (Bal et al 1995b). Thus, the spindle waves are slowly transformed into a paroxysmal oscillation that resembles that which occurs during spike-and-wave seizures.

In the intact animal, the cerebral cortex also plays an important, and perhaps even dominant, role in the generation of spike-and-wave seizures (Avoli et al 1990b, Steriade et al 1994). One hypothesis is that abnormal burst discharges in the cerebral cortex result in the pronounced excitation of thalamic reticular neurons. Together, the activity of these two regions may result in the strong excitation of and subsequent inhibition of thalamocortical cells, which could then result in large rebound bursts that feed into the hyperexcitable cortical network and thalamic reticular nucleus to reinitiate the next cycle of neuronal discharge.

NEUROTRANSMITTER MECHANISMS UNDERLYING THE TRANSITION FROM SLEEP TO WAKING

The transition from sleep to waking, or REM sleep, is associated with the depolarization of thalamocortical and thalamic reticular neurons (Hirsch et al 1983, Steriade et al 1986). Because the ascending systems of the brain stem (and hypothalamus) are critical to this transition (e.g. Bremer 1938, Moruzzi & Magoun 1949), the release of neurotransmitters from these neurons may be responsible for this depolarization. The search for ascending neurotransmitter systems that innervate the thalamus has identified at least five candidates:

acetylcholine (ACh) from the pedunculopontine and lateral dorsal tegmental nuclei, norepinephrine (NE) from the locus coeruleus, serotonin (5-HT) from the raphe nuclei, histamine (HA) from the tuberomammillary nucleus of the hypothalamus, and glutamate (reviewed in Steriade & McCarley 1990, McCormick 1992).

The investigation of each of these neurotransmitters reveals that the activation of muscarinic receptors by ACh, α_1-adrenoceptors by NE, and H_1 receptors by HA and metabotropic glutamate receptors results in the prolonged depolarization of thalamocortical neurons as a result of a reduction in a resting leak K^+ conductance termed I_{KL} (McCormick & Prince 1987, 1988; McCormick 1991; McCormick & Williamson 1991; McCormick & von Krosigk 1992). Activation of each of these receptors results in a slow depolarization of the membrane potential that results in an inhibition of rhythmic or rebound burst firing through the inactivation of I_T and the promotion of single-spike firing by bringing the membrane potential closer to the single-spike firing threshold (Figure 8*F*). Maximal activation of any combination of these receptors appears to result in a maximal response of a shift, or nearly complete shift, from rhythmic burst firing to just into the single-spike firing mode, suggesting that this response exhibits a ceiling that prevents it from causing thalamocortical neurons to fire at high rates merely from the release of modulatory transmitters.

A prominent response in thalamocortical neurons is the enhancement of the hyperpolarization-activated cation current I_h by a shift in its activation curve to more positive membrane potentials, thereby causing more of this current to be activated at each membrane potential negative to approximately -55 mV (reviewed in McCormick 1992). This response occurs following the activation of serotoninergic, β-adrenergic, and H_2-histaminergic receptors and the application of nitric oxide donors, and may be mediated by the activation of adenylyl cyclase (McCormick & Pape 1990b, McCormick & Williamson 1991, Pape & Mager 1992). Activation of purinergic A_1 receptors has the opposite effect: It shifts the voltage dependence of I_h to more negative membrane potentials (Pape 1992). Positive shifts in the voltage dependence of I_h increase the frequency of intrinsic oscillations and also reduce the ability of the cells to oscillate in both thalamocortical cells maintained in vitro and in computational models (McCormick & Pape 1990b, Soltesz et al 1991, McCormick & Huguenard 1992).

Together, these results suggest that the release of ACh, NE, glutamate, HA, and perhaps nitric oxide onto thalamocortical neurons should abolish sleep-related activity in thalamocortical networks and facilitate the single-spike activity typical of the waking state. Indeed, application of many of these substances to the A-laminae of the ferret LGNd results in a suppression of spindle wave generation in vitro (Lee & McCormick 1996a,b).

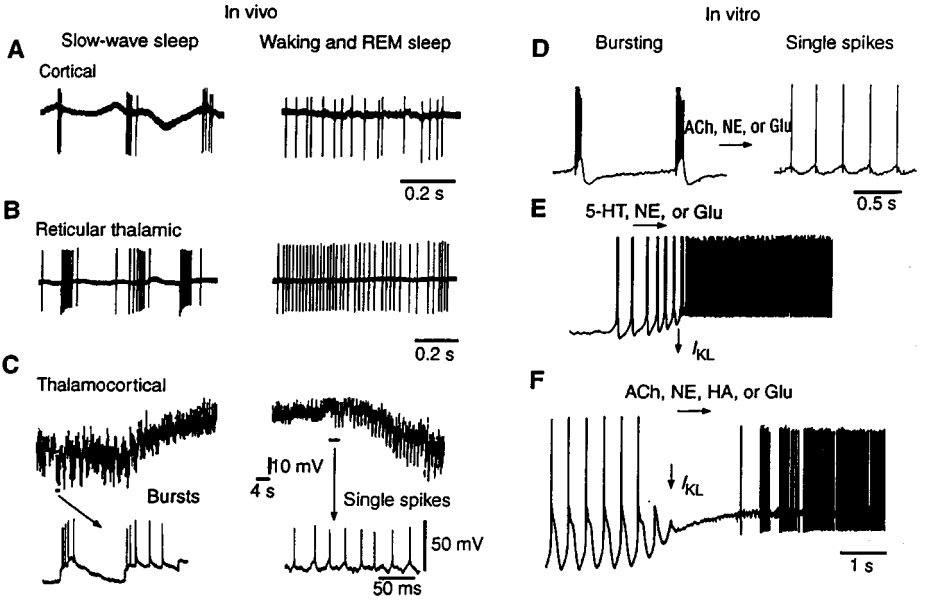

Figure 8 State-dependent activities in cortical and thalamic neurons. (*A–C*) Neurons in the cerebral cortex (*A*), thalamic reticular nucleus (*B*), and thalamic relay nuclei (*C*) change their activities in vivo from periodic and rhythmic spike bursts during natural, slow-wave sleep to tonic firing of trains of single spikes during waking and REM sleep in behaving cats with chronic implants. (*D–F*) Similar changes in firing pattern occur in vitro in neurons in the cerebral cortex (*D*), thalamic reticular nucleus (*E*), and thalamic relay nuclei (*F*) in response to various neurotransmitters released by modulatory systems. The depolarization results from the reduction of K^+ conductances and the enhancement of I_h. (From Steriade et al 1993, McCormick 1992, Hirsch et al 1983.)

The GABAergic neurons of the thalamic reticular and perigeniculate nuclei are modulated in a manner that is similar, but also distinct, from that of thalamocortical cells. Activation of serotoninergic 5-$HT_{2/1C}$, α_1-adrenergic, metabotropic glutamate, or CCK_A receptors on these neurons results in a marked and slow depolarization owing to the reduction of I_{KL} (McCormick & Wang 1991, Bal & McCormick 1993, Cox et al 1995) (Figure 8*E*). As in thalamocortical neurons, this depolarization of thalamic reticular cells results in a suppression of rhythmic burst firing and the promotion of single-spike activity. In contrast to this depolarizing response, the application of cholinergic agonists to perigeniculate and thalamic reticular neurons results in a rapid nicotinic excitation followed by a more prolonged muscarinic inhibition through the activation of a K^+ conductance (McCormick & Prince 1986b, Lee & McCormick 1995). Recent investigations reveal that the activation of noradrenergic, serotoninergic,

metabotropic glutamate, and CCK receptors on the GABAergic perigeniculate neurons results in the suppression of spindle wave generation and the promotion of single-spike activity (Lee & McCormick 1996a,b).

Activation of ascending pathways in vivo complement and extend these findings. The electrical stimulation of ascending cholinergic systems, or cholinergic projections from the basal forebrain, results in muscarinic inhibition in perigeniculate and thalamic reticular neurons that may be preceded by rapid nicotinic excitation (Hu et al 1989a, Pinault & Deschênes 1992b). In thalamocortical cells, electrical stimulation in the region of cholinergic neurons of the brain stem results in a rapid nicotinic excitation followed by a slow muscarinic depolarization (Hu et al 1989b, Deschênes & Hu 1990b, Curró Dossi et al 1991). Activation of ascending cholinergic systems is associated with the abolition of spindle and slow waves in the EEG and with the enhancement of higher-frequency activities, as occurs in the natural transition to waking or REM sleep (Curró Dossi et al 1991, Steriade et al 1993a).

Electrical stimulation in the region of the locus coeruleus also results in a slow excitation of thalamocortical cells (see Kayama 1985) and a block of slow rhythms in thalamocortical systems—an effect that is blocked by administration of α_2-antagonists, presumably by inhibiting the release of NE (Steriade et al 1993a). In addition, lesion of the locus coeruleus or administration of α_1-antagonists results in a marked reduction in the firing rate of thalamic reticular neurons (Pinault & Deschênes 1992a).

Together, these results suggest that the transition from the EEG-synchronized sleep to the waking state is associated with depolarization of thalamocortical neurons through multiple mechanisms, including increased barrages of fast EPSPs from prethalamic and corticothalamic systems; the reduction of I_{KL} from the release of ACh, NE, HA, and glutamate; and the enhancement of I_h through the release of 5-HT, NE, HA, and other agents. Simultaneously, the GABAergic cells of the thalamic reticular and perigeniculate nuclei are also depolarized through the release of 5-HT, NE, glutamate, and CCK. Since the synaptic release of most, if not all, of these agents increases with the transition from EEG-synchronized sleep to arousal (reviewed in Steriade & McCarley 1990, McCormick 1992), it is reasonable to suggest that they are responsible for the transition of thalamic neurons from the rhythmic burst firing to tonic mode of action potential generation. Presumably, the inhibitory influence of cholinergic fibers to the thalamic reticular and perigeniculate nuclei helps to temper these depolarizing influences and provides a mechanism for phasic disinhibition of thalamocortical neurons during, for example, shifts in attention or arousal.

The shift from EEG-synchronized sleep to REM sleep is also associated with an abolition of delta and spindle waves, as well as a marked reduction of

the occurrence of absence seizures, even though this state is associated with a marked inhibition of neuronal activity in noradrenergic, serotoninergic, and histaminergic neurons (reviewed in Steriade & McCarley 1990, McCormick 1992). The depolarized state of thalamocortical neurons at this state is presumably the result of the influence of ascending cholinergic and descending corticothalamic activity. The depolarization of thalamic reticular cells may result from the combined influence of increased tonic firing in both thalamocortical and corticothalamic systems.

The changes that occur in cortical circuits in the transition from EEG-synchronized sleep to waking and the actions of neuromodulatory transmitters on different types of cortical neurons appear to be considerably more complex than in the thalamus, perhaps owing to the wide variety of different cell types and neuronal circuits. Some cortical neurons do, however, exhibit burst discharges preferentially during sleep, and tonic single-spike activity during waking (Figure 8*A*) (reviewed in McCormick 1992). Interestingly, the application of ACh, NE, or a glutamate metabotropic receptor agonist to intrinsically burst-generating neurons (which typically are subcortically projecting large layer-V pyramidal cells) results in a depolarization through the reduction of a leak potassium current and a suppression of burst discharges, as occurs in the thalamus (Wang & McCormick 1993). This switch from burst generation to tonic firing is associated with an increase in linearity of the membrane responses of layer-V pyramidal cells (McCormick et al 1993). The excitability of non-burst-generating pyramidal cells may also be typically enhanced through the application of modulatory transmitters such as ACh, NE, 5-HT, or HA. This enhanced excitability results from a reduction in spike frequency adaptation owing to a block of the Ca^{2+}-activated K^+ current I_{AHP} and the voltage-dependent K^+ current I_M (McCormick & Prince 1986a, McCormick & Williamson 1989; reviewed in McCormick 1992). However, in addition to these increases in excitability, the activation of other receptors results in inhibitory responses.

SUMMARY

Neuronal activity in thalamocortical systems changes in parallel with changes in the state of the animal. During periods of EEG-synchronized sleep, groups of thalamic and cortical neurons interact during the generation of synchronized oscillations such as spindle waves and of slow oscillations. This network activity is generated as a consequence of both the intrinsic membrane properties of the constituent cells and their synaptic interactions. The low-threshold Ca^{2+} current is important in the generation of at least some of these network oscillations. The transition from EEG-synchronized sleep to arousal is accomplished through a depolarization of thalamic neurons, resulting in an

inhibition of the low-threshold Ca^{2+} current and an abolition of sleep-related oscillations. The depolarized state facilitates the transmission of information through the thalamus in a manner that is consistent with the awake and attentive state.

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