Thalamocortical Oscillations in the Sleeping and Aroused Brain

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Sleep is characterized by synchronized events in billions of synaptically coupled neurons in thalamocortical systems. The activation of a series of neuromodulatory transmitter systems during awakening blocks low-frequency oscillations, induces fast rhythms, and allows the brain to recover full responsiveness. Analysis of cortical and thalamic networks at many levels, from molecules to single neurons to large neuronal assemblies, with a variety of techniques, ranging from intracellular recordings in vivo and in vitro to computer simulations, is beginning to yield insights into the mechanisms of the generation, modulation, and function of brain oscillations.

The brain spontaneously generates complex patterns of neural activity (*1*). This dance of perceptual and motor activity within populations of neurons changes abruptly when the brain falls asleep. The rapid patterns characteristic of the aroused state are replaced by low-frequency, synchronized rhythms of neuronal activity. At the same time, electroencephalographic (EEG) recordings shift from low-amplitude, high-frequency rhythms to large-amplitude, slow oscillations (*2*). The dramatic reduction in forebrain responsiveness during sleep, the pervasiveness of these changes, and the discovery of the underlying specific cellular mechanisms all suggest that sleep oscillations are highly orchestrated and highly regulated. In recent years, the substrates of sleep-related oscillations, the mechanisms of their suppression during brain arousal, and the implications of these changes for forebrain function have begun to be understood from the molecular to the cellular and network levels.

The EEG oscillations that occur during sleep and arousal are generated in the thalamus and cerebral cortex, two regions that are intimately linked by means of reciprocal projections. The thalamus is the major gateway for the flow of information toward the cerebral cortex and is the first station at which incoming signals can be blocked by synaptic inhibition during sleep. This mechanism contributes to the shift that the brain undergoes as it changes from an aroused state, open to signals from the outside world, to the closed state of sleep (*3*).

Since 1980, major progress has been made in investigating the mechanisms of generating rhythmic activity in thalamocortical systems. These studies have demonstrated that although some isolated neurons can oscillate by virtue of their intrinsic properties (*4*), these oscillations of isolated neurons can be transformed by interactions with other neurons into less stereotyped rhythmic patterns (*5*). Indeed, in the intact brain many different types of sleep rhythms can be produced and generated in complex combinations (Fig. 1).

Here, we discuss the mechanisms of the generation of slow and fast oscillations in thalamocortical networks (*6*) in the sleeping and aroused brain, their control by neuromodulatory transmitter systems, and their influence on the normal and abnormal functions of the forebrain. The early stage of quiescent sleep is associated with EEG spindle waves, which occur at a frequency of 7 to 14 Hz; as sleep deepens, waves with slower frequencies (0.1 to 4 Hz) appear on the EEG. The other sleep state, associated with rapid eye movements (REM sleep) and dreaming episodes, is characterized by an abolition of low-frequency oscillations and an increase in cellular excitability, very much like wakefulness (*3*) although motor output is markedly inhibited (*7*).

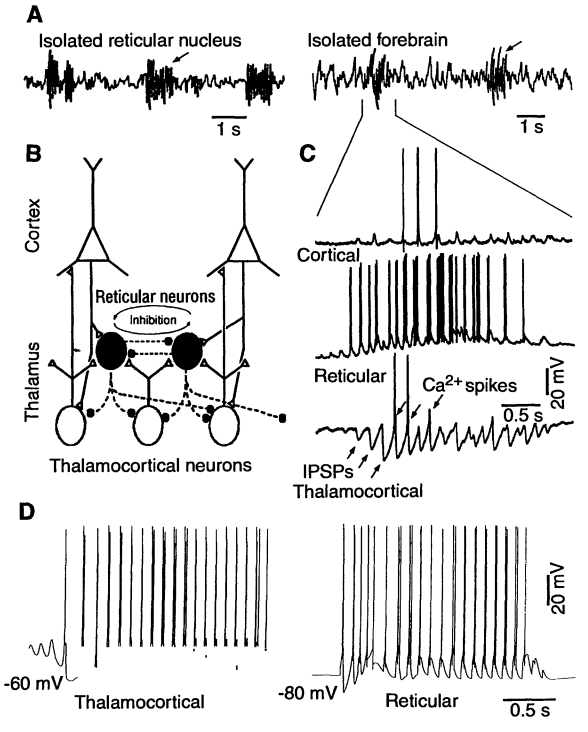

Fig. 1. Sleep spindle oscillations as synaptically generated in the thalamus. (**A**) (Left) Field potentials recorded in vivo through a microelectrode inserted in the deafferented reticular thalamic nucleus of a cat. Arrow indicates one spindle sequence. (Right) Spindle oscillations recorded in vivo through a microelectrode inserted in the intralaminar centrolateral thalamic nucleus of a cat with an upper brainstem transection, creating an isolated forebrain preparation. Note the two spindle sequences (the second marked by an arrow) and, between them, lower frequency (delta) waves. (**B**) Schematic diagram of neuronal connections involved in the generation of spindle oscillations. (**C**) Intracellular recordings of one spindle sequence [see (A)] in three neuronal types (cortical, reticular thalamic, and thalamocortical) of cats in vivo. (**D**) Computer model of 8- to 10-Hz spindle generation in a pair of interconnected thalamocortical and reticular neurons. The spindle is initiated by a shift in the voltage dependence of I_h as the concentration of intracellular Ca^{2+} is reduced. A burst of spikes in the thalamocortical cell excites the reticular thalamic cell, which in turn hyperpolarizes and produces a rebound burst in the thalamocortical neuron [as in vivo (C)]. The spindle is terminated by a shift of the voltage dependence of I_h as the concentration of intracellular Ca^{2+} increases. The waxing subthreshold oscillations in the thalamocortical neuron (before spindle bursting) are not present in vivo, and the interactions between reticular and thalamocortical cells are weaker so that the thalamocortical cell does not fire on every post-inhibitory rebound. Data for these figures were taken from (*16, 66*), (*13*), and (*12*) [(A), (B), and (C), respectively].

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The mechanisms that underlie the oscillations of the intact brain have been investigated primarily by intracellular recording from neurons with identified input-output organization in preparations in which the neuronal connections are preserved. In vitro brain slices have been used to elucidate the ionic conductances that contribute to the oscillatory properties of neurons. The most information could be gained by simultaneous intracellular and extracellular recordings in multiple sites of thalamic nuclei and neocortical areas. However, the complexity of these networks exceeds by far the power of recordings and analyses in electrophysiological studies. It may, however, be possible to use computer simulations to study rhythms similar to those observed in living animals by using realistic models of interacting cortical (*8*, *9*) and thalamic networks (*10*, *11*).

Falling Asleep: Spindle Waves

Spindle oscillations consist of waxing-and-waning field potentials of 7 to 14 Hz, grouped in sequences that last for 1 to 3 s and recur once every 3 to 10 s (Fig. 1A). The EEG spindles are the epitome of brain electrical synchronization at the onset of sleep, an electrographic landmark for the transition from waking to sleep that is associated with loss of perceptual awareness. These oscillations are generated in the thalamus as the result of synaptic interactions in a network in which the main players are the inhibitory [γ-aminobutyric acid (GABA)–containing] neurons of the reticular thalamic nucleus, thalamocortical cells, and cortical pyramidal neurons (Fig. 1B). Different areas of the cerebral cortex receive inputs from various dorsal thalamic nuclei. In turn, cortical neurons of layer 6 innervate topographically appropriate regions of both the dorsal thalamus and the reticular thalamic nucleus. The reticular cells receive excitatory inputs from axon collaterals of thalamic neurons that project to the cortex and of cortical neurons that project to the thalamus; they project back to the thalamus (but not to the cerebral cortex) and also innervate other cells of the reticular thalamic nucleus (*5*). In this manner, the reticular nucleus is uniquely positioned to influence the flow of information between the thalamus and cerebral cortex.

Intracellular recordings of reticular and thalamocortical cells in vivo (*5*, *12*) and in vitro (*13*) as well as computational modeling of thalamic cells (*11*) showed a mirror (inverse) image in these two neuronal classes during spindle oscillations (Fig. 1, C and D). In reticular cells, rhythmic (7 to 14 Hz) bursts are generated by low-threshold Ca^{2+} spikes and are superimposed on a slowly rising and decaying depolarizing envelope. The bursts of reticular cells inhibit large numbers of thalamocortical cells through their divergent GABA-containing axons, which leads to the appearance of rhythmic (7 to 14 Hz) inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons (Fig. 1C). Some of these IPSPs result in enough removal of inactivation of the low-threshold Ca^{2+} current to be followed by a rebound Ca^{2+} spike (*14*) and an associated burst of action potentials (Fig. 1C). These periodic bursts in thalamocortical cells converge onto reticular neurons and facilitate their rhythmic oscillation. The bursts are also transferred to the cortex, where they induce excitatory postsynaptic potentials (EPSPs) in cortical pyramidal cells, thereby generating the EEG spindle waves.

Isolation of the reticular nucleus from the rest of the thalamus and cerebral cortex abolishes spindle oscillations in the dorsal thalamus and the cortex (*15*), but it is important that the deafferented reticular thalamic nucleus can itself generate spindle oscillations (*16*). Indeed, the reticular thalamic cells possess a unique assortment of ionic currents that allows them to individually oscillate in the frequency range of spindles (*17*). Axonal and, in some species, dendrodendritic (*18*) interconnections between reticular cells may allow the coupling and interaction of these endogenous oscillators, thereby generating spindle oscillations in an isolated nucleus (*16*). This hypothesis is strengthened by simplified models of reticular thalamic neurons with mutual inhibition that exhibit synchronous oscillatory activity (*19*).

What causes the waxing-and-waning pattern of spindle waves? We speculate that the waxing of the spindle oscillations could be generated by a recruitment of neurons through divergence of axonal connections between reticular and thalamocortical neurons as well as through the effects of cortical pyramidal cells that are entrained in the oscillation and impinge back onto reticular thalamic neurons. The waning of spindle oscillations is more difficult to understand. Shifts in the properties of ionic conductances during the oscillation itself may be responsible, as demonstrated in a simplified model (Fig. 1D). Another possibility is that there is a progressive failure of participation of individual elements in the pacemaking reticular thalamic nucleus and, consequently, a decreased release of GABA in the dorsal thalamus. Spindle oscillations are generated by interactions between neurons with different intrinsic cellular properties; computer models allow us to dissect the contributions of each cellular and network mechanism.

Absence Seizures as a Perversion of Spindle Oscillations

The spindle oscillations of natural sleep are related to the development of a peculiar pattern of oscillatory activity, the spike-and-wave EEG complexes, which are associated with absence (petit mal) epileptic seizures (*20*). Because the reticular thalamic nucleus is central to the genesis of spindle oscillations (*15*, *16*), decreasing or abolishing the inhibitory efficacy of reticular neurons upon thalamocortical cells would also decrease the incidence of epileptic spike-and-wave discharges (*21*). This hypothesis is supported by recent experiments that show that, in animals with genetic absence epilepsy, thalamic injections of a selective agonist of $GABA_B$ receptors increase the incidence of spike-and-wave discharges, whereas injections of a $GABA_B$ antagonist decrease these seizures in a dose-dependent manner (*22*). The activation of $GABA_B$ receptors in thalamocortical cells enhances the removal of inactivation of the low-threshold Ca^{2+} spike and subsequently results in larger than usual rebound burst discharges in a greater than usual proportion of thalamocortical cells (*13*). These facilitated rebound bursts further excite reticular cells, which quickly results in the generalization of paroxysmal activity. The ability of $GABA_B$ antagonists to block absence seizures and the finding that some of the drugs commonly used to treat absence seizures reduce the amplitude of the low-threshold Ca^{2+} spike (*23*) lend pharmacological support to this hypothetical nature of absence seizure generation.

Delta and Slow Sleep Oscillations

During the late stages of sleep, spindle oscillations are progressively reduced and replaced by thalamocortical oscillations with slower frequencies. Recent intracellular analyses revealed two different oscillations with distinct origins and cellular mechanisms: One of them is termed delta oscillation (1 to 4 Hz) and the other is termed slow oscillation (<1 Hz).

Delta waves were initially shown to arise between cortical layers 2 to 3 and 5 (*24*). Intracellular recordings in vivo (*25*, *26*) and in vitro (*27*, *28*) indicate that the thalamus is also involved in the generation of this rhythm (Fig. 2, A and B). In contrast to the origin of spindle oscillations in synaptic networks, a delta-frequency rhythm can be generated in single cells by the interplay of two intrinsic currents of thalamocortical neurons—the hyperpolarization-activated cation current (I_h) and the transient low-threshold Ca^{2+} current (also known as I_t)—in much the same manner that single sinoatrial cardiac cells

generate rhythmic contractions (29). A wide variety of other ionic currents with different voltage dependencies and kinetics of activation and inactivation contribute to the generation of rhythmic activity, particularly in the shaping of the amplitude and time course of each burst of action potentials, as revealed both through biological experiments and computational modeling (Fig. 2).

The hyperpolarization of thalamocortical cells is a critical factor for the interplay between I_h and I_t that generates delta oscillation. After disconnection from related cortical areas, thalamocortical neurons are hyperpolarized by about 10 mV (because of the absence of the depolarizing corticothalamic input) and, consequently, display a spontaneous, self-sustained delta oscillation (25, 26). Direct depolarization of oscillating cells induces tonic, irregular firing, whereas removal of the steady depolarizing current sets the neurons back into the delta oscillatory mode (Fig. 2A). The dependence of delta oscillation on membrane hyperpolarization was also seen in simulations of thalamic neurons (Fig. 2C).

Delta oscillations occur when the thalamocortical cells are more hyperpolarized than they are during spindle oscillations (25). This suggested that thalamocortical cells undergo a progressive hyperpolarization from drowsiness and the early stages of sleep, when spindles prevail in the EEG, to the late sleep stages, when delta waves are predominant. The mutual exclusivity between spindle and delta oscillations in intracellular recordings (25, 30) explains the common EEG finding in humans and animals that early sleep stages are characterized by the presence of spindle rhythms, whereas delta waves overwhelm scarcely visible spindles during late stages of sleep (31).

However efficiently the intrinsic currents promote delta rhythmicity in single thalamocortical neurons, this oscillation would not become synchronized in large neuronal assemblies and thus would not be visible in the EEG without network synchronizing factors (25). Synchronization may be achieved by local mechanisms (32, 33), or another, more general way of synchronizing is realized by the widespread connections from the reticular nuclear complex to other thalamic nuclei. Corticothalamic volleys potentiate and synchronize the delta oscillation of simultaneously recorded thalamic cells (25). Thalamic synchronization can be induced by stimulating cortical foci that are not directly connected to the thalamic nuclei where the recordings are performed; this recruitment of thalamic cells may be achieved through reticular thalamic connectivity (25). In simulations of thalamocortical cells oscillating in the bursting mode at delta frequency, cortical inputs are easily able to reset the cell to a new phase of its rhythm (34).

The slow oscillation (<1 Hz) (Fig. 3) was recently discovered in intracellular studies of neocortical cells (35, 36). Cortical pyramidal neurons from layers 2 to 6 and in numerous (sensory, motor, and associational) areas display rhythmic depolarizing envelopes on which action potentials are superimposed. The data indicate that the slow depolarizations are due to synaptic inputs, a component of which is mediated by *N*-methyl-D-aspartate (NMDA) receptors; it was suggested that a persistent Na^+ current is also involved. Because in a subpopulation of neurons the slow oscillation consisted of rhythmic groups of short-lasting IPSPs (35), it was assumed that not only pyramidal cells but also inhibitory, local-circuit cells display this rhythm. The depolarizations were separated by long-lasting hyperpolarizations and were synchronous with grouped EEG waves recurring at the same frequency (<1 Hz, mainly 0.2 to 0.5 Hz) (Fig. 3). Simultaneous recordings of cells demonstrated synchronous inhibitory periods in the intra- and extracellularly recorded neurons (35).

The survival of this slow oscillation after extensive thalamic lesions (36) suggests that it is generated within the neocortex. However, the synchronization of cortical neurons is a powerful source for driving both reticular and thalamocortical neurons (37), with the consequence of grouping the other sleep rhythms (spindle and delta oscillations) within this frequency range (Fig. 3). It was proposed that the rhythmic dampening (approximately every 3 s) of delta-frequency potentials in thalamocortical cells (Fig. 3) is due to an increase in membrane conductance resulting from the periodic (approximately 0.3 Hz) impingement of cortical excitatory and reticular thalamic inhibitory inputs.

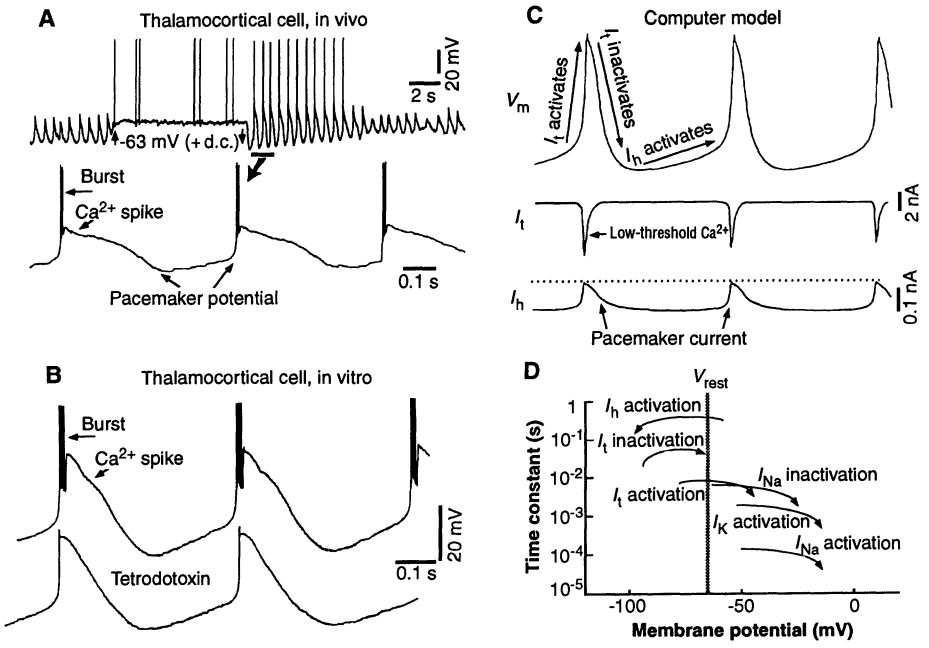

Fig. 2. Intrinsic cellular mechanisms of thalamic delta oscillation. (**A**) Voltage dependency of delta oscillation. Shown is the intracellular recording in vivo of a lateroposterior thalamocortical neuron after decortication of areas projecting to that nucleus in an anesthetized cat. The cell oscillated spontaneously at 1.7 Hz. A 0.5-nA depolarizing current (+ d.c.) pulse (between arrows), bringing the membrane potential to −63 mV, prevented the oscillation, and its removal set the cell back into the oscillatory mode. Three cycles marked by the horizontal bar in the upper trace are expanded below. (**B**) Spontaneous rhythmic burst firing in a cat lateral geniculate relay cell recorded in vitro before and after block of voltage-dependent Na^+ conductances with application of the Na^+ channel blocker tetrodotoxin. (**C**) Computational model of rhythmic generation of I_t as a consequence of interplay between I_t and the pacemaker current I_h. V_m, membrane potential. (**D**) Diagram of activation and inactivation for the primary ionic currents in thalamocortical cells. Each arc represents the time constant for activation or inactivation of a voltage-dependent current. Most currents begin to activate (or inactivate) on the left side of the arc and are fully activated (or inactivated) on the right side. One exception is the cation current I_h, which activates with hyperpolarization and does not inactivate. Different combinations of currents are active at different membrane potentials. The voltage-dependent NA^+ current, I_{Na}, and the delayed-rectifier K^+ current, I_K, are responsible for the fast action potentials; V_{rest} is the resting potential. Data for these figures were taken from (25), (27), (10), and (65) [(A), (B), (C), and (D), respectively].

Functional Consequences of Sleep Oscillations

One major consequence of the shift from waking to sleep is the greatly reduced influence of peripheral sensory input on forebrain neurons (*3*). The patterns of activity in the corticothalamic circuits during sleep are instead generated from within. This is most dramatically illustrated in the state of REM sleep, during which dreams occur (*7*). Despite great interest, there is no generally accepted function for dreams or, for that matter, for the sleep state itself (*38*).

A clue to why there are slow oscillations during sleep can be found in the cellular mechanisms that generate them. The low-threshold Ca^{2+} current I_t is mostly inactivated at the depolarized potentials of thalamocortical cells during waking and REM sleep (*5*). During the generation of spindle oscillations and slow-wave sleep, the thalamocortical cells hyperpolarize and consequently depolarizing pulses of Ca^{2+} enter, which may trigger enzyme cascades as well as have longer lasting effects on gene regulation. Thalamocortical and cortical neurons may use oscillations as a way to homeostatically adjust the balance of ionic currents and regulatory mechanisms (*39*). The rhythmic spike bursts during sleep may also maintain the forebrain neurons in a state of biochemical readiness for a quick transition to an aroused state (*40*).

During quiescent (non-REM) sleep, the thalamus excites the cortex with patterns of activity that are more spatially and temporally coherent than would normally be encountered in the awake state. This widespread activity could be used to reorganize cortical networks: just as the biochemical activity within single neurons might be homeostatically regulated, so too could the patterns of synaptic connectivity within networks (*37, 41*). In addition, learning during waking may lead to spurious brain states that could be systematically edited and reorganized during sleep (*42, 43*).

Cellular Mechanisms of Transition from Sleep to Arousal

Brainstem lesions in humans cause coma (*44*), which suggests that there are neuronal systems in the brainstem that are essential for maintaining normal states of vigilance. Indeed, electrical activation of certain tegmental regions in the brainstem mimics arousal (*45*) by suppressing spindle waves (*5, 46*), delta waves (*25*), and slow cellular rhythms (*47*) in sleep and replacing these low-frequency oscillations with activity similar to that seen in an awake, attentive state. Various ascending activating systems are localized in the upper brainstem, posterior hypothalamus, and basal forebrain and release a variety of neurotransmitters, including acetylcholine (ACh), norepinephrine (NE), serotonin (5-HT), histamine (HA), and glutamate (*7, 48*). These systems collectively innervate the entire expanse of cerebral cortex, thalamus, and other structures and therefore have a widespread influence on forebrain function (*49*).

These neurotransmitter systems abolish the low-frequency rhythms in thalamocortical systems during waking and REM sleep as well as promote more tonic activity or the appearance of high-frequency oscillation (*5*). The firing rates of neurons in different ascending modulatory nuclei all increase in anticipation of awakening (*50*). The effects of the putative neurotransmitters released by ascending activating systems, as revealed by in vivo and in vitro experiments, confirm that all these neurotransmitters help maintain the waking state and, for ACh, also the dreaming state. An especially clear example of this is found in the thalamus, where both thalamocortical and reticular thalamic cells exhibit activity that differs in sleep and arousal (Figs. 4 and 5). The changes in firing between sleep and arousal are accomplished by depolarization of the membrane potential by 5 to 20 mV, which inactivates the low-threshold Ca^{2+} current and therefore inhibits burst firing (Figs. 4 and 5). Electrical stimulation in the region of brainstem cholinergic and noradrenergic neurons, or direct application of

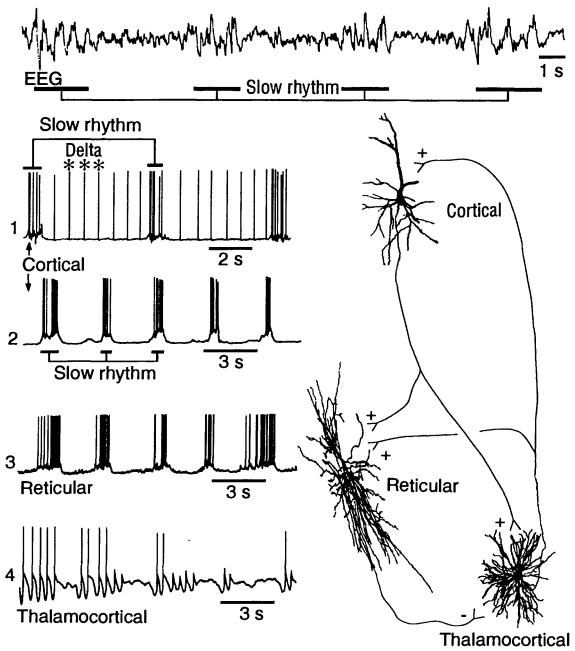

Fig. 3. The slow cortical rhythm and its reflection in thalamic neurons. (**Top**) Surface EEG recording of the slow (0.2 Hz) rhythm of delta waves in a chronically implanted, naturally sleeping cat; periodic sequences of delta waves, recurring with a slow rhythm, are marked by the horizontal bars. (**Below**) Intracellular recordings of four neurons in anesthetized cats. From top to bottom: two pyramidal cortical cells (1 and 2), one reticular thalamic cell (3), and one thalamocortical cell (4). Intracellularly stained cortical and thalamic neurons are illustrated at right [data taken from (*35*) and (*67*)]. Neuron 1 from cortical association area 5 displays the slow rhythm (0.16 Hz) and, between the slow depolarizing events, regular action potentials (asterisks) recurring at the delta (1.6 Hz) frequency arising in thalamocortical cells (Fig. 2, A and B). Cortical cell 2 exhibits the slow rhythm at 0.3 Hz. Reticular thalamic cell 3 oscillates at 0.3 Hz synchronously with the slow cortical rhythm. Thalamocortical neuron 4 in the ventrolateral nucleus oscillates within the delta frequency (2.5 Hz) (which tends to dampen and is periodically revived) within the frequency range of the slow rhythm (0.2 to 0.3 Hz) [data taken from (*35–37*)]

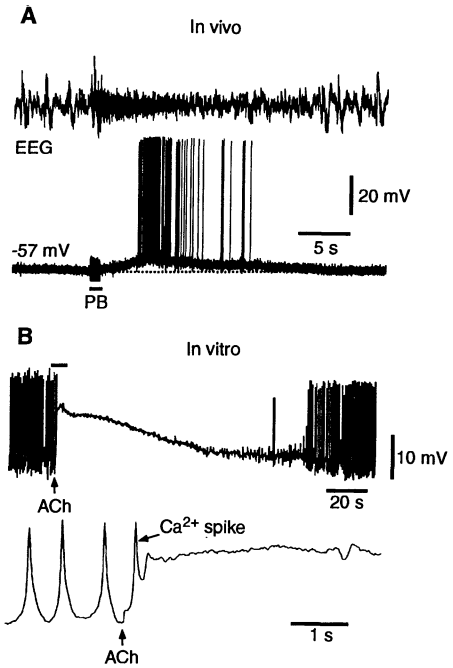

Fig. 4. Brainstem cholinergic activation of thalamocortical cells. (**A**) Stimulation of the brainstem peribrachial (PB) cholinergic area produces long-lasting (approximately 15 s) depolarization and spike discharges in an intracellularly recorded, ventrolateral thalamocortical cell simultaneously with an activation response (with a similar time course) of the EEG recorded from the motor cortex in vivo. (**B**) Suppression of rhythmic generation of low-threshold Ca^{2+} spikes in a thalamic relay neuron by application of ACh. (Below) Expansion of the initial portion (marked by the horizontal bar in the upper trace) of the ACh-induced effect. Data for these figures were taken from (*51*) and (*52*) [(A) and (B), respectively].

ACh or NE, results in prolonged depolarization of thalamocortical cells, which is associated in vivo with a disruption of sleep rhythms (Fig. 4) (*25*, *51*, *52*); NE and 5-HT, on the other hand, depolarize reticular cells (Fig. 5) (*53*). These transmitter-induced depolarizations result from reduction of a specialized K^+ conductance termed I_{KL} that, at least in thalamocortical cells, is coupled to muscarinic ACh and α_1-adrenergic receptors (*52*) by means of G proteins that are not sensitive to pertussis toxin. Functionally, switching from rhythmic burst generation to more tonic activity enhances participation in sensory-motor processing such that the percentage of EPSPs that result in the generation of action potentials increases (*54*) and the propensity to generate low-frequency, synchronized oscillations characteristic of sleep and of absence epilepsy is abolished (*3*, *7*, *20*).

Changes in the activity patterns generated by cortical neurons and circuits are less stereotyped than those of thalamic cells and circuits, although some common features exist. The low-frequency oscillations of the cortical EEG disappear upon arousal and are replaced by higher frequency (20 to 80 Hz, mainly around 40 Hz) rhythms (*25*, *55*). As in the thalamus, these alterations in cortical activity take place, at least in part, by depolarization of pyramidal cells (*47*), presumably through the reduction of specialized K^+ conductances by ACh, NE, and other neuromodulators (Fig. 5, A and D) (*56*).

The high-frequency (20 to 80 Hz) oscillations in the EEG occur during some behaviors such as immobility during hunting in cats and focused attention to stimuli during complex sensory or motor tasks in monkeys (*57*). Other studies have shown the existence of such high-frequency, synchronized rhythms in sensory systems (*58*). Neurons throughout the nervous system (for example, the retina, lateral geniculate thalamic nucleus, and cortex) have the ability to generate repetitive trains of action potentials in the frequency range of 20 to 80 Hz (*33*, *59*), although the synchronization of this activity into behaviorally relevant subgroups of widely spaced neurons has been demonstrated only in the cerebral cortex (*58*). In humans, higher frequency oscillations have been recorded by magnetoencephalography not only during the awake state, but also during REM sleep (*60*). The approximately 40 Hz, coherent magnetoencephalographic rhythm may involve the intralaminar thalamic nuclei (*60*), which contain thalamocortical neurons that show depolarization-dependent 40-Hz spike bursts during both waking and REM sleep (*61*).

The diversity of cortical cells and their complex interactions make it difficult to model cortical networks with the same confidence with which thalamic networks have been modeled. It is not, however, difficult to generate oscillatory activity in the 20- to 80-Hz range with networks of simplified neurons (*62*). These models have revealed the need to regulate the tendency of recurrent networks to oscillate. The excitability of neurons can be controlled by inhibition; however, inhibition is also an efficient mechanism for synchronizing large populations of pyramidal neurons because of voltage-dependent mechanisms in their somas and the strategic location of inhibitory boutons on the somas and the initial segments of axons, where action potentials are initiated (*9*). Realistic simulations of cortical neurons demonstrate that sparse excitatory connectivity between distant populations of neurons can produce synchronization within one or two cycles but only if the long-range connections are made on inhibitory as well as excitatory neurons (*63*).

Conclusions

Despite the complexity of brain rhythms, we are beginning to understand how they arise from the intrinsic behavior of single neurons and the propensity of coupled neurons to form large-scale oscillatory states. Not only does the brain exhibit coherent activity at a variety of frequencies, ranging from less than 1 Hz to over 40 Hz, but the extent of its spatial coherence is also quite variable, from localized clusters of neurons at the higher frequencies (*58*) to states that may involve the entire neocortex at the lowest frequencies (*35–37*) during slow sleep rhythms and absence epilepsies. It is also becoming clear that inhibitory neurons in the thalamus and the cortex are of particular importance in producing the synchrony and in controlling the spatial extent of the coherent populations. Neuromodulatory systems are capable of shifting thalamocortical networks between different oscillatory states (*7*, *48*).

Synchrony and other network properties could be exploited for controlling the flow of information between brain areas and for deciding where to store important information. Getting neurons to fire together is a potent way of enhancing their impact on other neurons, because the synaptic inputs arriving synchronously on a neuron produce greater output than the same number of inputs arriving asynchronously. If too many neurons fire together at the same time, this amplification may go awry and lead to an epileptic seizure. Therefore, the level of activity and degree of synchrony within neural networks are strongly regulated through dynamic cellular mechanisms.

Just as the various peripheral organs of the body must be regulated by various neurotransmitter and neuropeptide systems to efficiently meet the behavioral demands of the organism, we envision that the ascend-

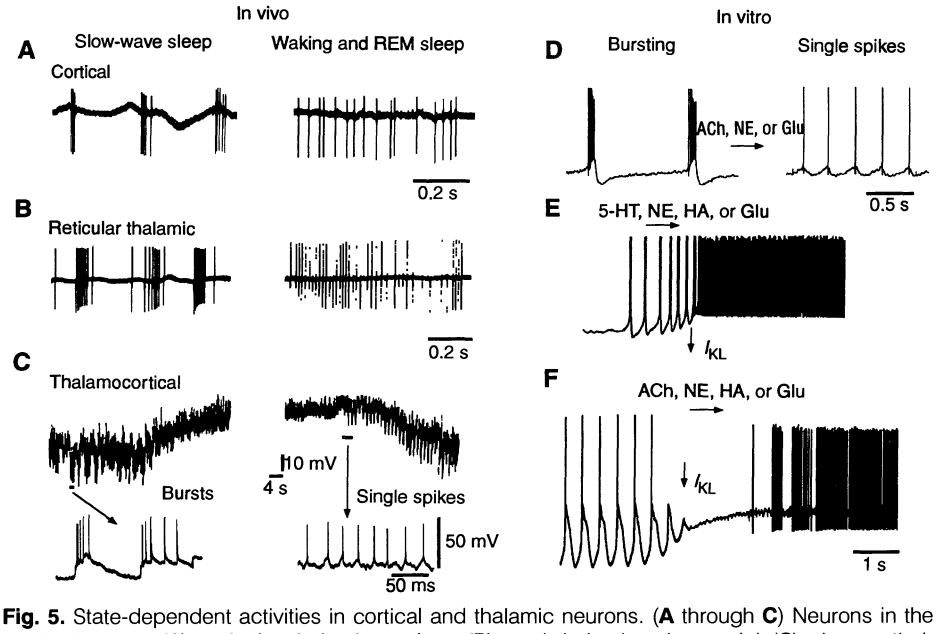

Fig. 5. State-dependent activities in cortical and thalamic neurons. (**A** through **C**) Neurons in the cerebral cortex (A), reticular thalamic nucleus (B), and thalamic relay nuclei (C) change their activities in vivo from periodic and rhythmic spike bursts during natural, slow-wave sleep to tonic firing of single spikes during waking and REM sleep in chronically implanted, behaving cats. (**D** through **F**) Similar changes in firing pattern occur in these neurons (from the cerebral cortex, reticular thalamic nucleus, and thalamic relay nuclei, respectively) in vitro in response to various neurotransmitters released by modulatory systems. The depolarization results from the reduction of ionic conductances (for example, I_{KL}). Data for (A) were taken from (*42*); for (B), from (*68*); for (C), from (*69*); for (D), from (*56*); for (E), from (*53*); and for (F), from (*27*)].

ing modulatory transmitter systems delicately tune the state and excitability of the different parts of the nervous system so that it is appropriate for the analysis of sensory information, the cognitive processing and storage of this information, and the subsequent performance of the appropriate neuronal and behavioral responses (*64*). Dynamical changes in the oscillatory activity of the brain are indicative of these ongoing modulatory processes and changing states of the underlying neural circuits. Uncovering and modeling the cellular mechanisms of these dynamic changes may provide important clues to long-standing questions ranging from the functional role of sleep to the nature of cognitive representations.

REFERENCES AND NOTES

1. The term "spontaneous" applies to processes that are not triggered by detectable stimuli. The condition of being spontaneous (or self-sustained), used to define EEG rhythms, should not be regarded as strictly separated from the domain of electrical events that are evoked (or induced) by various stimuli. Indeed, in addition to their informational (phasic) functions, sensory signals are at the origin of a tonic background that steadily sustains brain excitability. That activity in central structures outlasts the incoming messages and maintains the cerebral tonus was proposed long ago [J. von Uexkull, *Zeit. Biol.* **50**, 168 (1904); F. Bremer, *C. R. Soc. Biol.* (*Paris*) 118, 1235 (1935)].
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6. The thalamocortical network comprises a series of "building blocks" defined by their patterns of connectivity and functions. Some of these building blocks are (i) reciprocal excitation (dorsal thalamic cells releasing excitatory amino acids and driving cortical neurons, which, in turn, excite dorsal thalamic cells through the same neurotransmitters); (ii) recurrent inhibition (dorsal thalamic cells exciting reticular thalamic neurons, which use a potent inhibitory transmitter and, in turn, project back and inhibit dorsal thalamic cells); (iii) reciprocal inhibition (between reticular thalamic cells); and (iv) parallel excitation and inhibition (corticothalamic cells that, on one hand, directly excite dorsal thalamic neurons and, on the other hand, indirectly inhibit dorsal thalamic neurons through prior excitation of reticular thalamic cells).
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Neuronal Mechanisms of Object Recognition

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Recognition of objects from their visual images is a key function of the primate brain. This recognition is not a template matching between the input image and stored images like the vision in lower animals but is a flexible process in which considerable change in images, resulting from different illumination, viewing angle, and articulation of the object, can be tolerated. Recent experimental findings about the representation of object images in the inferotemporal cortex, a brain structure that is thought to be essential for object vision, are summarized and discussed in relation to the computational frames proposed for object recognition.

Almost 30 visual areas have been identified in the cerebral cortex of the macaque monkey, and many of them can be organized into two anatomical pathways: the ventral pathway directed toward the inferotemporal cortex (IT) and the dorsal pathway directed toward the inferior parietal lobule. The two pathways are also functionally distinguishing: The ventral pathway is thought to be responsible for object vision, and the dorsal pathway for space vision or visuomotor control (*1*). The ventral pathway runs from cortical area V1 to V2, thereafter to V4, and finally to the IT. This pathway is thought to be essential for object vision because monkeys that have had their IT bilaterally ablated show severe and selective deficits in learning tasks that require the visual recognition of objects (*2*). The IT is further divided into the posterior IT, or TEO, and the anterior IT, or TE. The projection from V4 that terminates in TEO is more dense than that to TE, and TEO projects to the most posterior-anterior extent of TE. The IT projects to various structures outside the visual cortex, including the perirhinal cortex (areas 35 and 36), the prefrontal cortex, the amygdala, and the striatum of the basal ganglia. The projections to these targets are more numerous from TE, especially the anterior part of TE, than from the areas at earlier stages. Therefore, there is a sequential cortical pathway from V1 to TE, and outputs from the pathway originate mainly in TE.

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Columnar Organization in TE

An obstacle in the study of neuronal mechanisms of object vision has made the determination of the stimulus selectivity of individual cells difficult: There is a great variety of object features in the natural world, and if perception is based on a calculation that is nonlinear (which is very plausible), the variety cannot be represented by an arbitrary set of "basic" features. We developed a systematic reduction method in which the study of selectivity was started with many natural objects, and the complexity of the effective stimuli was reduced to determine the features critical for activation of individual cells (*3, 4*). Some previous studies