

What Stops Synchronized Thalamocortical Oscillations?

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Summary

Slow-wave sleep as well as generalized absence seizures are characterized by the occurrence of synchronized oscillations in thalamocortical systems that spontaneously appear and disappear. The spontaneous appearance of synchronized oscillations results from the initiation by one or a small number of cells followed by the progressive recruitment of large numbers of neighboring neurons into the synchronized network activity. Synchronized network oscillations representative of slow-wave sleep, as well as absence seizures, were demonstrated to cease spontaneously at least in part through the persistent activation of a hyperpolarization-activated cation conductance. Block of this conductance resulted in oscillations that, once generalized, occur continuously. These results indicate that the persistent activation of a hyperpolarization-activated cation conductance is a key mechanism through which synchronized oscillations in thalamocortical networks normally terminate.

Introduction

Widespread synchronized oscillations occur throughout the thalamus and cerebral cortex during periods of slow wave sleep (Steriade et al., 1993; Niedermeyer and Lopes da Silva, 1993; Steriade et al., 1994), as well as during generalized absence seizures (Niedermeyer, 1990; Steriade et al., 1993). One prototypical example of these synchronized oscillations is spindle waves. During slow wave sleep, spindle waves appear as 7 Hz–14 Hz synchronized oscillations in thalamocortical networks that wax and wane over a 1 s–3 s period (Andersen and Andersson, 1968; Steriade and Deschênes, 1984; Steriade et al., 1993). These synchronized oscillations are generated in the thalamus largely through a simple reciprocal interaction between the GABA (γ -aminobutyric acid)-containing neurons of the thalamic reticular/perigeniculate nuclei and the thalamocortical cells of the corresponding recipient zones of the thalamus (Steriade and Deschênes, 1984; Steriade et al., 1993; von Krosigk et al., 1993; Bal et al., 1995a, 1995b).

The thalamic reticular nucleus is a collection of GABAergic neurons that forms a shell surrounding the dorsal and lateral aspects of the thalamus (Jones, 1985). These cells give rise to dense axonal innervations of thalamocortical cells in localized regions of the thalamus

(for example, see Uhlich et al., 1991; Cox et al., 1996). The axons of thalamocortical cells, in turn, give rise to axon collaterals within the thalamic reticular nucleus as the parent axon passes through en route to the cerebral cortex (Friedlander et al., 1981; Harris, 1987). The perigeniculate nucleus (PGN) is interconnected with the dorsal lateral geniculate nucleus and is functionally equivalent to the thalamic reticular nucleus.

Burst firing in the GABAergic neurons of the thalamic reticular/perigeniculate nuclei during the generation of spindle waves results in GABA_A receptor-mediated inhibitory postsynaptic potentials (IPSPs) in thalamocortical cells (Steriade and Deschênes, 1984; Bal et al., 1995a, 1995b). These phasic IPSPs in thalamocortical cells result in the removal of inactivation of the low-threshold Ca²⁺ current. The rising, or repolarizing, phase of the IPSP then activates this Ca²⁺ current resulting in the generation of a low-threshold Ca²⁺ spike and a burst of action potentials (Bal et al., 1995a, 1995b). Burst firing in thalamocortical cells once again excites the GABAergic cells of the thalamic reticular or perigeniculate nuclei, thus starting the next cycle of the spindle oscillation (Bal et al., 1995a, 1995b). In this manner, spindle waves are generated through a simple reciprocal interaction between the GABAergic cells of the thalamic reticular/perigeniculate nuclei and their corresponding thalamocortical neurons.

Spindle waves occur spontaneously at the rate of about once every 3 s–20 s and are characterized by a gradual growth (waxing) and decrement (waning) over the 1 s–3 s of their duration (Steriade et al., 1993; Bal et al., 1995a, 1995b). The 3 s–20 s period in between individual spindle waves is characterized by a relative refractory period during which the threshold for the generation of additional spindle waves is raised considerably (Kim et al., 1995). Analyses of the cellular mechanisms of generation of absence seizures suggest that they share many of the cellular mechanisms responsible for the generation of spindle waves (Avoli et al., 1990; Steriade et al., 1993). In particular, individual absence seizures suddenly appear and disappear and are followed by a relative refractory period (Niedermeyer, 1990; Avoli et al., 1990; Steriade et al., 1993).

Intracellular recordings *in vitro* suggest that spindle waves initiate through the activation of one or more thalamic reticular/PGN or thalamocortical neurons. Generalization of this activity to large portions of the thalamocortical network follows spindle wave initiation (Kim et al., 1995). In contrast to the mechanisms for initiation and spread of spindle waves, the events responsible for their “waning” are less clear. Previously, we have suggested that spindle waves may spontaneously wane through the progressive hyperpolarization of the GABAergic neurons of the PGN (von Krosigk et al., 1993). This progressive hyperpolarization of GABAergic neurons was proposed to result in a decreased response of these cells to excitatory postsynaptic potentials (EPSPs) arriving from burst firing in thalamocortical cells. However, extracellular and intracellular recordings obtained *in vivo* suggest that other mechanisms must also occur,

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since many thalamic reticular cells may not hyperpolarize during the generation of spindle waves (Mulle et al., 1986; Steriade et al., 1986).

Intracellular recordings and computational models of thalamocortical neurons suggested another possible mechanism for the cessation of synchronized oscillations. Single thalamocortical neurons are capable of generating rhythmic low-threshold Ca^{2+} spikes and associated bursts of action potentials at frequencies of 0.5 Hz–4 Hz. These oscillations are characterized by the regular occurrence of low-threshold Ca^{2+} spikes that are interspaced by a depolarizing “pacemaker potential” (McCormick and Pape, 1990a; Soltesz et al., 1991; Curró Dossi et al., 1992; McCormick and Huguenard, 1992). Activation of the h-current, a noninactivating mixed Na^+ and K^+ current that slowly activates upon hyperpolarization, appears to generate the depolarizing pacemaker potential (McCormick and Pape, 1990a). Intracellular studies and computational models demonstrate that the generation of these intrinsic oscillations, as well as network oscillations such as spindle waves, is critically dependent upon the amplitude, kinetics, and voltage dependence of the h-current. Persistent activation of the h-current can result in a progressive failure of thalamocortical neurons and neuronal networks to generate rhythmic oscillations (McCormick and Pape, 1990b; McCormick and Huguenard, 1992; Destexhe et al., 1996). Interestingly, intracellular recordings have revealed that single thalamocortical neurons are capable of generating waxing and waning oscillations apparently through intrinsic ionic mechanisms (Leresche et al., 1991), and it has been speculated that the waning of these oscillations is due to the persistent activation of the h-current.

The persistent activation of the h-current can result in a decrease in apparent input resistance of the cell as well as a depolarization of the membrane potential (McCormick and Pape, 1990a). Together, these can result in the inhibition of thalamocortical oscillations by promoting the inactivation of the low-threshold Ca^{2+} current and by reducing the amplitude of IPSPs generated by burst firing in thalamic reticular/PGN neurons. One possibility is that the rhythmic oscillations of the spindle wave results in a persistent activation of the h-current and this, in turn, results in the waning of the spindle wave itself by decreasing the ability of thalamocortical cells to generate rebound low-threshold Ca^{2+} spikes in response to burst firing in thalamic reticular/PGN neurons (McCormick, 1992; Destexhe et al., 1993a, 1993b). In this study, we demonstrate that, indeed, the persistent activation of I_h makes an important contribution to the cessation of synchronized network oscillations (Bal and McCormick, 1995, Soc. Neurosci., abstract).

Results

Intracellular recordings from thalamocortical neurons in the ferret dorsal lateral geniculate nucleus (LGNd) maintained *in vitro* revealed the spontaneous occurrence of spindle waves at the rate of approximately one every 5 s–20 s (Figure 1A), as reported previously (von Krosigk et al., 1993; Bal et al., 1995a, 1995b). These spindle

waves are characterized by the arrival of barrages of IPSPs at 6 Hz–10 Hz and the generation of a rebound low-threshold Ca^{2+} spike and burst of action potentials following every second to fourth IPSP (Figure 1A). Each spindle wave waxed and waned over a 2 s–4 s period and was followed by a small (1 mV–2.5 mV) slow afterdepolarization ($n = 21$) (Figure 1A).

Bath application of the GABA_A receptor antagonist bicuculline methiodide (20 μM) resulted in a transformation of normal spindle waves into paroxysmal events resembling those underlying absence seizures ($n = 15$) (Figure 1B), as reported previously (Bal et al., 1995a, 1995b; von Krosigk et al., 1993). These paroxysmal synchronized oscillations are characterized by the arrival of slow GABA_B receptor-mediated IPSPs and the generation of large rebound low-threshold Ca^{2+} spikes at the rate of ~ 2 Hz–4 Hz (Figure 1B) (Bal et al., 1995a, 1995b). The bicuculline-induced paroxysmal oscillations also exhibited a waxing and waning and a prolonged and small (1 mV–4 mV) depolarization of the membrane potential in between each network oscillation (Figure 1B). In addition, during the generation of both spindle waves and the bicuculline-induced slow oscillation, the negative-most membrane potential obtained by barrages of IPSPs arriving from the PGN became progressively more depolarized during approximately the second half of the oscillation (Figure 1). The duration of the slow afterdepolarization following the generation of the network oscillations matched the period between network oscillations (Figure 1).

The intracellular injection of hyperpolarizing current pulses revealed that the slow afterdepolarization following spindle waves was associated with a 14%–18% increase in apparent membrane conductance and a substantially decreased ability of these constant current pulses to generate rebound low-threshold Ca^{2+} spikes ($n = 6$) (Figure 2). As the slow afterdepolarization decreased in amplitude, the amplitude of the rebound low-threshold Ca^{2+} spike following the intracellular injection of the hyperpolarizing constant current pulse increased (Figure 2A).

To test whether or not a similar decreased responsiveness may occur in response to the arrival of IPSPs, we activated localized regions of either the PGN or interlaminar zones with pressure-pulse applications of glutamate. Our intracellular investigations of neurons in the interlaminar regions of the ferret LGNd have revealed that these cells function in a manner identical to those of the PGN. These interlaminar neurons exhibit electrophysiological properties that are indistinguishable from those of the PGN and form reciprocal interconnections with thalamocortical neurons in the relay lamina (von Krosigk et al., 1994, Soc. Neurosci., abstract). Activation of the GABAergic neurons in the PGN or in the interlaminar regions through the pressure-pulse application of glutamate (0.5 mM in micropipette) activated IPSPs that resulted in the generation of rebound low-threshold Ca^{2+} spikes (Figure 2B). As with hyperpolarizing current pulses, these IPSPs lost their effectiveness to generate rebound low-threshold Ca^{2+} spikes in thalamocortical neurons following the generation of spindle waves (Figure 2B). Compensation for the spindle wave afterdepolarization with the intracellular injection of current facilitated the return of activation of rebound low-threshold

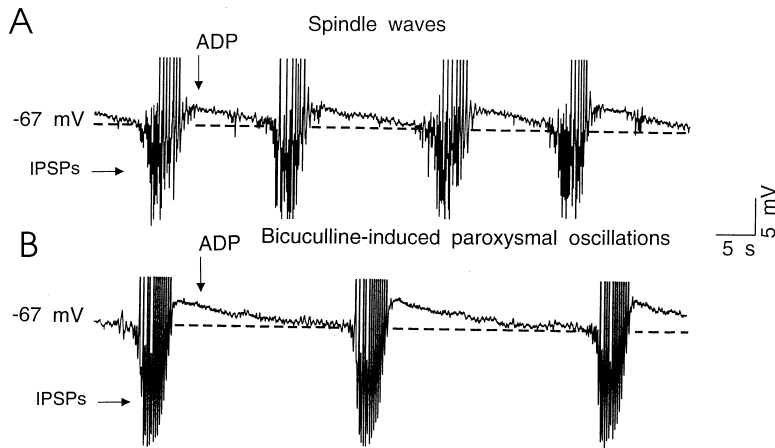


Figure 1. Spindle Oscillations Are Followed by a Slow Afterdepolarization

(A) Intracellular recordings from a thalamocortical relay neuron in lamina A of the ferret LGNd maintained as a sagittal slice in vitro. A slow afterdepolarization (ADP) occurs following the generation of a spindle wave. (B) Bath application of bicuculline methiodide (20 μ M) results in the transformation of spindle waves into a paroxysmal 2 Hz–4 Hz oscillation that resembles the cellular events underlying absence seizures. These bicuculline-induced paroxysmal oscillations also exhibit a waxing and waning appearance and are followed by a slow afterdepolarization. During both spindle waves and the bicuculline-induced paroxysmal oscillations, the peak amplitude of the IPSPs first increases and then decreases as the spindle wave waxes and wanes.

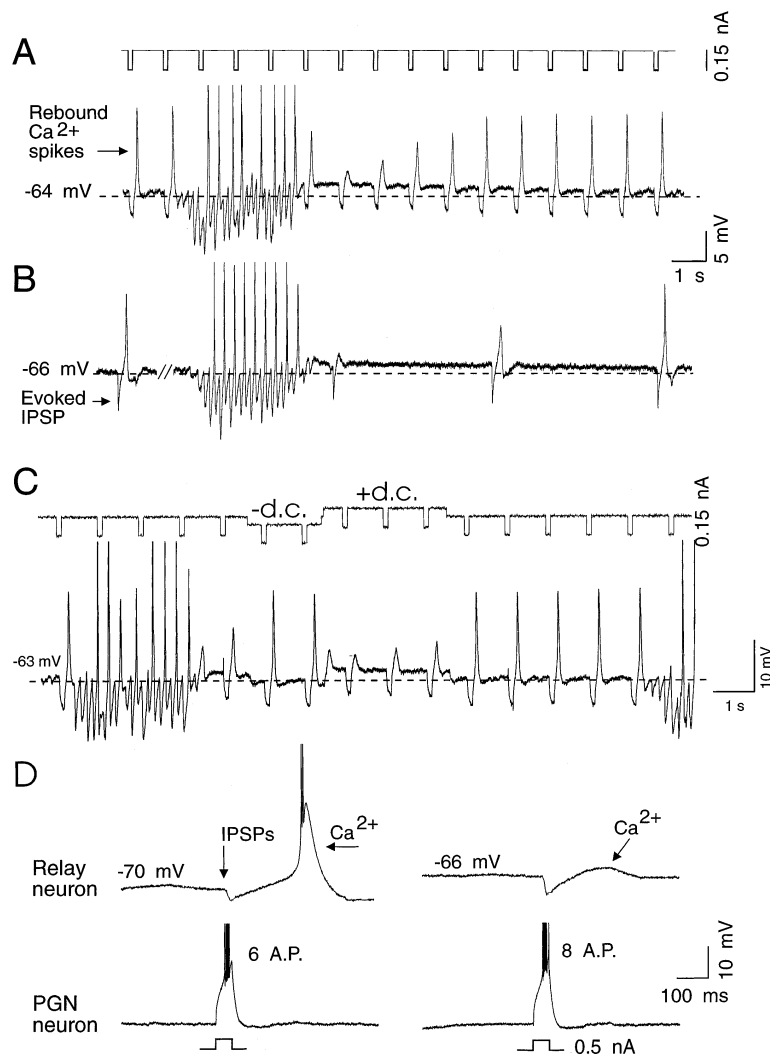


Figure 2. The Slow Afterdepolarization Reduces the Ability of Hyperpolarizations to Generate Rebound Ca^{2+} Spikes

(A) Intracellular injection of a short-duration (120 ms) hyperpolarizing current pulse is followed by the activation of a rebound low-threshold Ca^{2+} spike. The ability of this constant current pulse to generate a rebound Ca^{2+} spike is significantly reduced during the slow afterdepolarization that follows the generation of a spindle wave, owing in part to the depolarization of the cell and to the increase in apparent input conductance. (B) Activation of the GABAergic neurons of the interlaminar region with a local application of glutamate (0.5 mM in micropipette) results in an IPSP that activates a rebound low-threshold Ca^{2+} spike in the recorded thalamocortical neuron. Immediately following the generation of a spindle wave, the IPSP no longer evokes a rebound low-threshold Ca^{2+} spike during the slow afterdepolarization. The ability of the evoked IPSP to evoke a rebound Ca^{2+} spike recovers as the slow afterdepolarization ends. (C) The reduction in rebound Ca^{2+} spikes is due in part to changes in membrane potential. Immediately following the generation of a spindle wave, there is an afterdepolarization associated with the generation of reduced rebound Ca^{2+} spikes following the injection of hyperpolarizing current pulses. Compensation for the change in membrane potential during the slow afterdepolarization with the intracellular injection of hyperpolarizing current (-d.c.) reinstates the rebound Ca^{2+} spikes, even though the electrotonic response to the hyperpolarizing current pulse is reduced in amplitude. Similarly, depolarization of the cell by about 3 mV with the intracellular injection of current (+d.c.) greatly reduces the amplitude of the rebound Ca^{2+} spike. Returning the current injection to pre-spindle levels reinstates the rebound Ca^{2+} spikes just prior to the occurrence of the next spindle wave.

(D) Simultaneous intracellular recordings from monosynaptically connected PGN and thalamocortical neurons reveal that a burst of action potentials in the PGN neuron can activate a rebound low-threshold Ca^{2+} spike and burst of action potentials when the thalamocortical cell is at -70 mV, but this is markedly reduced by a small depolarization of the membrane potential to -66 mV.

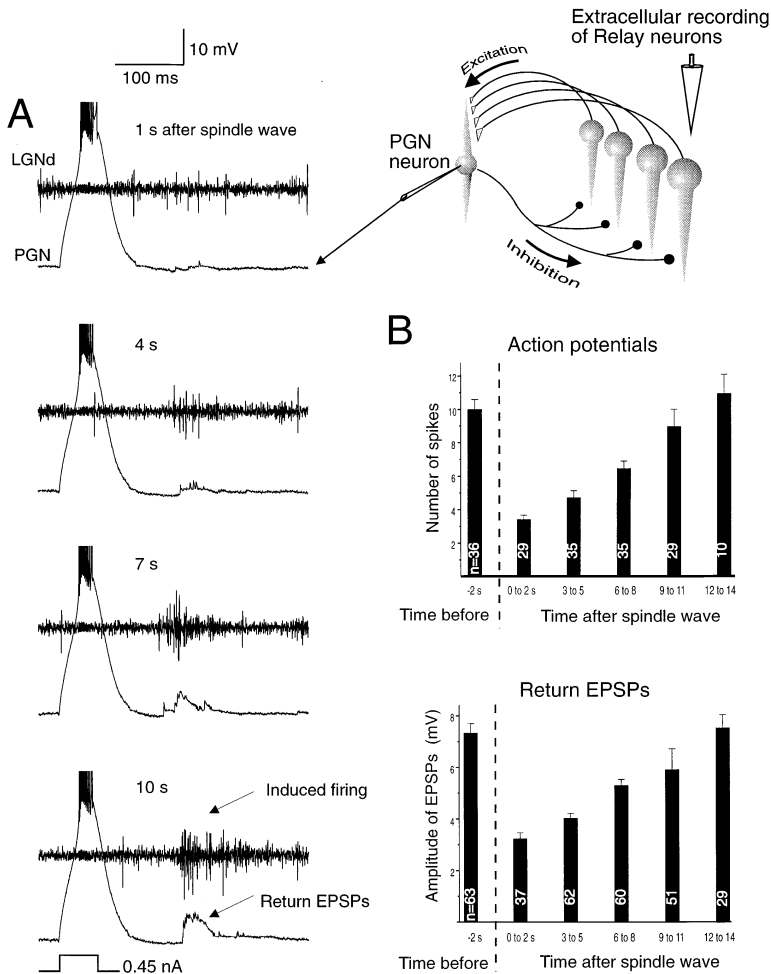


Figure 3. The Spindle Wave Refractory Period Is Associated with a Decreased Ability of Burst Firing in a Single PGN Cell to Induce a Rebound Burst of Action Potentials in Thalamocortical Relay Cells

(A) Intracellular injection of a short (50 ms) depolarizing current pulse into a PGN neuron is associated with a burst of action potentials in lamina A at a latency of ~120 ms–150 ms, presumably resulting from the generation of rebound low-threshold Ca^{2+} spikes in thalamocortical neurons (see Figure 2D). In addition, feedback EPSPs at a latency of ~125 ms–150 ms appear in the PGN neuron following the burst of action potentials.

(B) The occurrence of a spontaneous spindle wave is associated with a marked reduction in the intensity of rebound burst discharges in lamina A as well as in the amplitude of the return EPSPs. As the spindle wave refractory period ends, the amplitude of both the action potential bursts and return EPSPs gradually increases, until the next spindle wave is generated.

Ca^{2+} spikes following hyperpolarizing current pulses or glutamate-activated IPSPs, although these hyperpolarizing events were still smaller than usual owing to the increase in apparent input conductance (Figure 2C).

The possibility that small (2 mV–5 mV) depolarizations of the membrane potential may inhibit the generation of rebound low-threshold Ca^{2+} spikes was investigated either in single neurons during the injection of current pulses (for example, see Figure 2C) or through the performance of dual intracellular recordings from synaptically connected PGN and thalamocortical relay cells. Intracellular injection of small (5 mV–10 mV; 100 ms–150 ms duration) hyperpolarizing current pulses into thalamocortical relay cells at resting membrane potentials (–63 mV to –68 mV) was typically followed by the generation of rebound low-threshold Ca^{2+} spikes. Depolarization of the membrane potential through the intracellular injection of current by as little as 2 mV–5 mV typically abolished these rebound Ca^{2+} spikes or reduced their amplitude (Figure 2C) to such an extent that they no longer activated action potentials ($n = 4$). Similarly, dual intracellular recordings from monosynaptically coupled PGN and thalamocortical relay neurons revealed that the activation of a burst of action potentials in a single PGN cell may result in the generation of a rebound low-threshold Ca^{2+} spike in the postsynaptic thalamocortical neuron (Figure 2D). Depolarization of the thalamocorti-

cal cell by 2 mV–4 mV, i.e., by an amount similar to that associated with the spindle wave afterdepolarization, was sufficient to block the generation of rebound bursts of action potentials following the evoked IPSP (Figure 2D). These results suggest that the cessation of both spindle waves and the bicuculline-induced paroxysmal oscillation may result from the decreased ability of IPSPs arriving from the PGN neurons to generate rebound low-threshold Ca^{2+} spikes in thalamocortical neurons.

Examination of the PGN–LGNd–PGN Loop during the Refractory Period

Previously, we have demonstrated that activation of a single PGN neuron with the intracellular injection of a depolarizing current pulse was often sufficient to generate rebound burst firing in a number of thalamocortical neurons, resulting in the arrival of “return” EPSPs in the recorded PGN cell (Bal et al., 1995a, 1995b). We used this ability of PGN cells to activate return EPSPs coupled together with extracellular recordings from thalamocortical neurons in the A-laminae to test the hypothesis that the refractory period is associated with a decreased responsiveness of thalamocortical neurons to synaptic inputs generated by a burst of action potentials in a PGN neuron.

Just prior to the occurrence of a spindle wave, activation of a single PGN neuron resulted in the occurrence

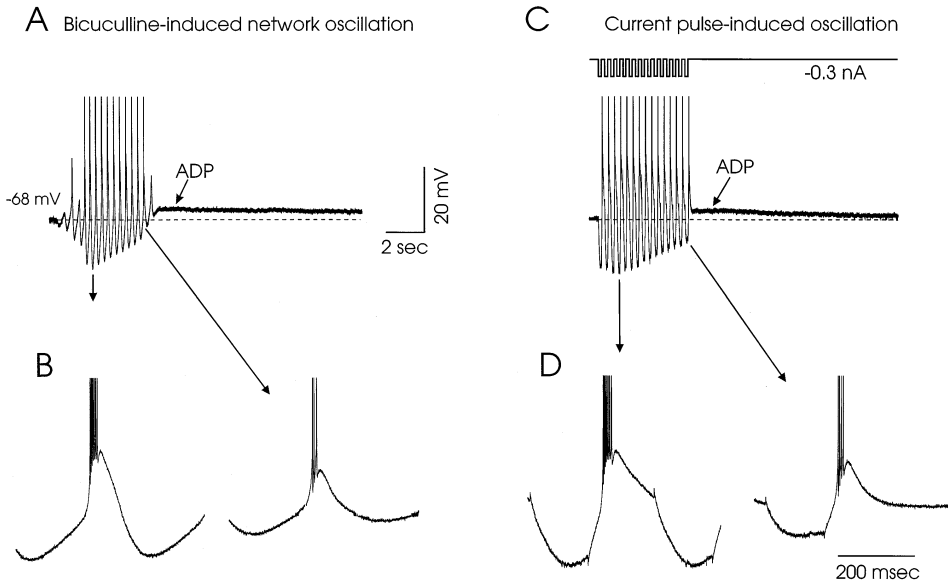


Figure 4. Repetitive Hyperpolarization through the Intracellular Injection of Current Pulses Mimics Some of the Effects of Network Oscillations on Thalamocortical Cells

(A) Intracellular recording from a thalamocortical cell during the generation of a bicuculline-induced paroxysmal network oscillation. The oscillation is associated with an increase, followed by a pronounced decrease in the peak amplitude of the IPSPs, as well as the rebound low-threshold Ca^{2+} spikes in the thalamocortical neuron.

(B) Two rebound sequences are expanded for detail.

(C) The intracellular injection of repetitive hyperpolarizing current pulses in this neuron results in a progressive decrease in the amplitude of the electrotonic response to each current pulse and a subsequent marked decrease in the amplitude of the rebound low-threshold Ca^{2+} spike (expanded in [D] for detail). Following the cessation of the current pulses is an afterdepolarization (ADP) similar to that associated with the generation of the bicuculline-induced network oscillation.

of return EPSPs resulting from rebound burst firing of inhibited thalamocortical relay cells ($n = 11$) (Figure 3A, 10 s). Extracellular multiple unit recordings from the appropriate portion of the LGNd revealed that these return EPSPs were associated with a burst of action potentials from presumed thalamocortical neurons ($n = 4$ pairs) (for example, see Figure 3A, 10 s). The generation of a spontaneous spindle wave was associated with a marked decrease in the intensity or amplitude of both the burst of action potentials at the extracellular recording site ($n = 4$) as well as the barrage of return EPSPs ($n = 11$), despite the generation of the same number and frequency of action potentials in the PGN neuron (Figures 3A and 3B). As the time since the generation of the spindle wave increased, the induced burst of action potentials in the thalamocortical cells and the subsequent return EPSPs grew in amplitude until the generation of the next spontaneous spindle wave (Figures 3A and 3B). These results further support the hypothesis that the waning of spindle waves and the generation of the refractory period is mediated by a markedly diminished ability of a burst of action potentials in PGN neurons to induce a rebound low-threshold Ca^{2+} spike in thalamocortical cells.

Mechanism of Generation of the Decreased Responsiveness and Afterdepolarization

Thalamocortical neurons exhibit a slowly activating and deactivating cation current, I_h , that is activated with hyperpolarization (McCormick and Pape, 1990a). We tested the possibility that the reduced responsiveness of thalamocortical neurons to repetitive IPSPs and the

generation of the slow afterdepolarization may be due to the activation of I_h through the intracellular injection of repetitive hyperpolarizing current pulses. Intracellular injections of 80 ms–250 ms duration repetitive hyperpolarizing current pulses at frequencies of 2 Hz–8 Hz into single thalamocortical neurons mimicked some of the features of the network oscillations. In particular, the intracellular injection of repetitive hyperpolarizing current pulses was associated with a progressive decrease in the amplitude of the electrotonic response to each constant current pulse and the generation of a slow afterdepolarization ($n = 11$) (Figures 4–6). The slow afterdepolarization was associated with a 15%–28% increase in membrane conductance, after compensation for the depolarization with the intracellular injection of direct current (d.c.) ($n = 6$) (data not shown).

During the generation of the bicuculline-induced slow oscillation, the amplitude of each rebound low-threshold Ca^{2+} spike progressively decreased as the network oscillation waned (Figures 4A and 4B). Similarly, the amplitude of rebound low-threshold Ca^{2+} spikes generated in response to hyperpolarizing current pulses also progressively decreased as the peak amplitude of the membrane deviation achieved by each hyperpolarizing constant current pulse decreased (Figures 4C and 4D). The afterdepolarizations following the bicuculline-induced oscillation and the mimicked oscillation induced with repetitive hyperpolarizing current pulses were similar in amplitude and duration (Figures 4–6).

The effect of the slow afterdepolarization on the participation of the cell in the network oscillation was examined by injecting repetitive hyperpolarizing current

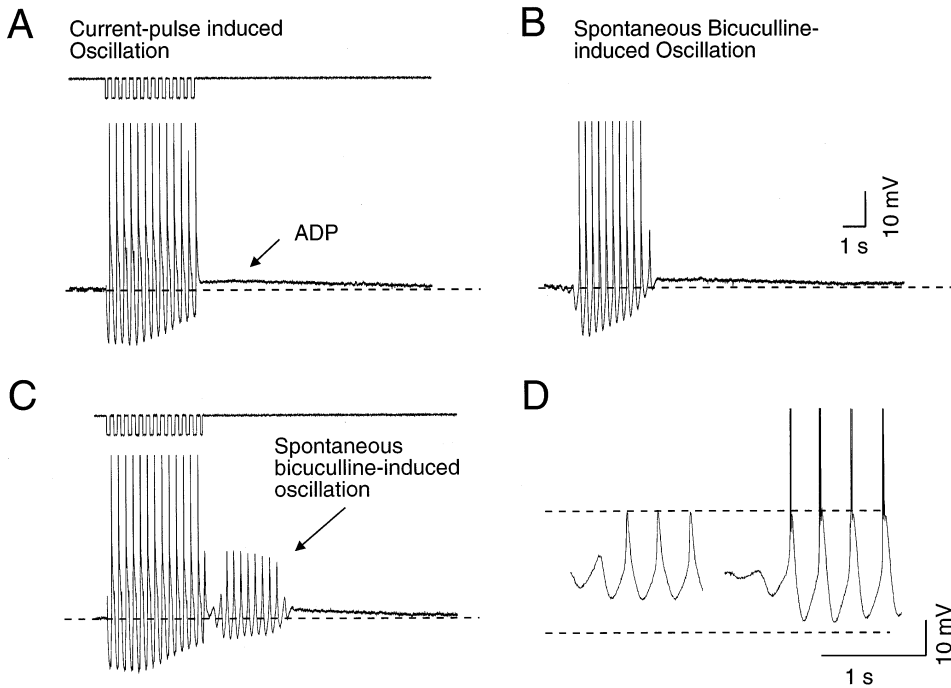


Figure 5. The Slow Afterdepolarization Induced during Repetitive Hyperpolarization Reduces the Participation of the Thalamocortical Cell in Network Oscillations

(A) Intracellular injection of repetitive hyperpolarizing current pulses results in a progressive decrease in the peak amplitude of the electrotonic response as well as in the generation of an afterdepolarization (ADP).

(B) The spontaneous occurrence of a bicuculline-induced paroxysmal oscillation is associated with repetitive burst firing and a slow afterdepolarization.

(C) When a network oscillation occurred during the afterdepolarization induced in the recorded cell with the intracellular injection of hyperpolarizing current pulses, the amplitude of the low-threshold Ca^{2+} spikes were reduced and no longer generated action potentials.

(D) Expansion of low-threshold Ca^{2+} spikes in (B) and (C) for detail.

pulses just prior to the spontaneous occurrence of a bicuculline-induced oscillation or a spindle wave ($n = 4$ cells) (Figure 5). In comparison with control, the rebound low-threshold Ca^{2+} spikes that occurred during a spindle wave or bicuculline-induced slow oscillation that is superimposed upon the slow afterdepolarization are markedly reduced in amplitude (Figure 5). This result indicates that the slow afterdepolarization following the intracellular injection of repetitive hyperpolarizing current pulses is capable of markedly reducing the ability of thalamocortical cells to participate in network oscillations.

The steady decrease in the peak amplitude achieved by the hyperpolarizing current pulses and the presence of an afterdepolarization suggests that these two properties may be due to tonic activation of the hyperpolarization-activated cation current I_h (McCormick and Pape, 1990b; McCormick and Huguenard, 1992). Here, we tested this possibility through the use of extracellular application of Cs^+ , a specific blocker of I_h (Mayer and Westbrook, 1983; McCormick and Pape, 1990a). Local (10 mM–20 mM in micropipette) or bath (0.5 mM–1 mM) application of Cs^+ resulted in a complete abolition of the slow afterdepolarization following repetitive hyperpolarizing current pulses ($n = 5$) (Figure 6A), a block of the depolarizing “sag” associated with each electrotonic

hyperpolarizing response (Figures 6B and 6C), and a block of the progressive decrease in the amplitude of the membrane potential achieved with each hyperpolarizing current pulse in the train (Figure 6A, cf. Normal and Cesium). Measurements of the duration of action potentials in the presence of Cs^+ revealed that they were unchanged in comparison with normal medium ($0.82 \text{ ms} \pm 0.11 \text{ ms}$; mean \pm SD; normal at action potential base; $0.81 \text{ ms} \pm 0.13 \text{ ms}$ cesium; $n = 5$).

An additional property of the hyperpolarization-activated cation current I_h is that it is deactivated with depolarization, with the rate of deactivation being proportional to the extent of depolarization (Mayer and Westbrook, 1983; McCormick and Pape, 1990a). Intracellular injection of a brief (1 s–2 s) depolarization into single thalamocortical neurons abolished the slow afterdepolarization that followed the injection of repetitive hyperpolarizing current pulses ($n = 3$) (Figures 6D and 6E), even though these depolarizations did not result in the generation of action potentials. The hyperpolarization that follows these depolarizations is mediated by the deactivation and reactivation of some portion of I_h (McCormick and Pape, 1990a). Together, these results indicate that the afterdepolarization following synchronized thalamic network oscillations may be generated through the persistent activation of I_h .

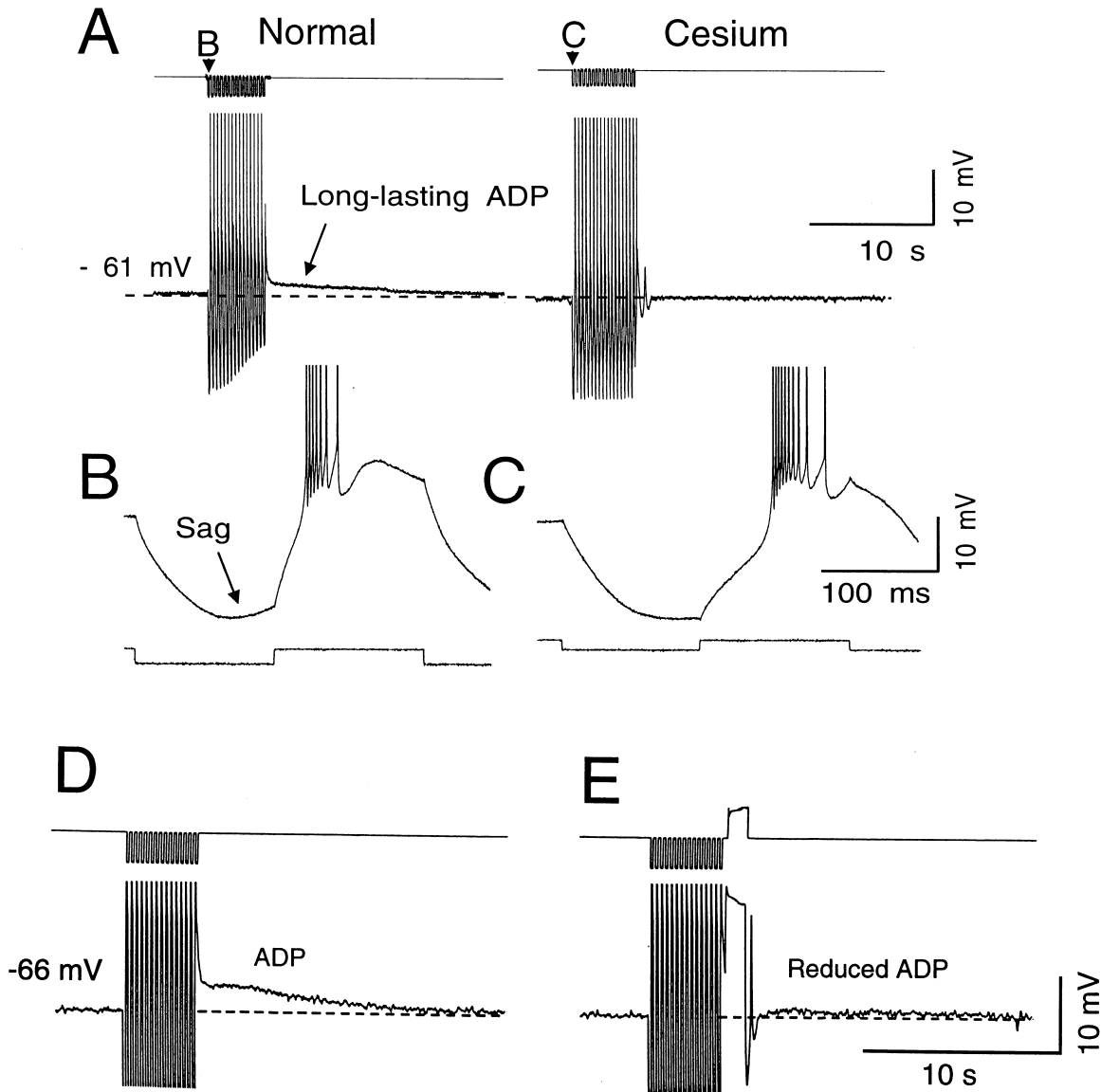


Figure 6. Persistent Activation of the Hyperpolarization-Activated Cation Current I_h Generates the Slow Afterdepolarization

(A) Intracellular injection of repetitive (4 Hz) short-duration (120 ms) hyperpolarizing current pulses results in the generation of a slow afterdepolarization (ADP). Local application of Cs^+ (20 mM in micropipette) completely, and reversibly, blocks this afterdepolarization.

(B) and (C) Expansion of electrotonic response to intracellular injection of hyperpolarizing current pulses, illustrating the effects of Cs^+ . The main effect was a block of the depolarizing sag that accompanies hyperpolarization, indicating block of I_h .

(D) and (E) Intracellular injection of a depolarizing current pulse to deactivate I_h also results in a block of the afterdepolarization. Intracellular injection of repetitive hyperpolarizing current pulses is followed by an afterdepolarization (D). Depolarization of the neuron during this afterdepolarization results in a reduction or abolition of the afterdepolarization (E). The full extent of the voltage deviations during the hyperpolarizing current pulses are not illustrated.

If the persistent activation of I_h is critical to the waning of spindle waves and the bicuculline-induced oscillation and the generation of the refractory period, then block of this current should result in a block of these network properties. Remarkably, bath application of Cs^+ (0.5 mM–2 mM) resulted in a progressive shortening of the spindle wave refractory period and a lengthening of the duration of individual spindle waves as I_h was blocked until these synchronized oscillations occurred continuously without cessation, as revealed with intracellular

($n = 4$) (Figures 7A–7C), and extracellular multiple unit recordings ($n = 6$) (data not shown). Identical results were obtained with local application of Cs^+ (10 mM–20 mM in micropipette) applied with pressure ejection ($n = 5$). In these experiments, the spindle wave refractory period was observed to decrease steadily as Cs^+ was applied and to recover within a few minutes following the cessation of Cs^+ application (data not shown). Intracellular recordings from individual thalamocortical cells revealed that either the bath or local application of Cs^+

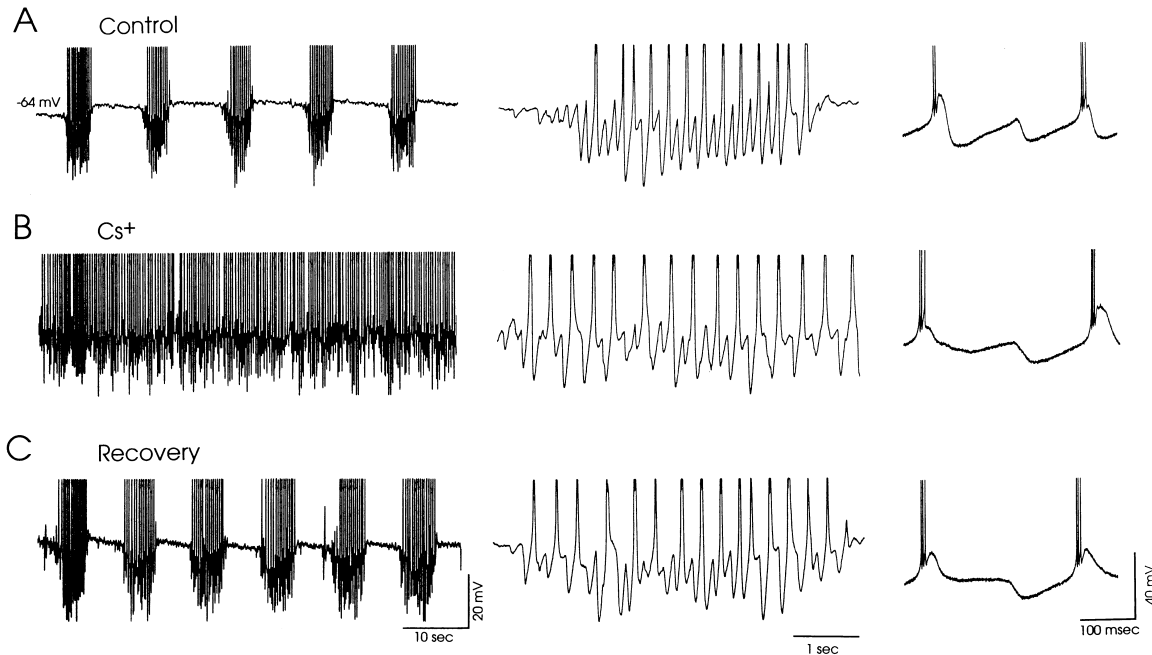


Figure 7. Application of Extracellular Cs⁺ Results in a Block of the Spindle Wave Refractory Period

(A) In normal bathing medium (control), spindle waves occur approximately once every 15 s. Expansion of one spindle wave in the middle trace illustrates the repetitive IPSPs and rebound Ca²⁺ spikes in this neuron. Expansion of two of these rebound Ca²⁺ spikes in the right-most trace illustrates their amplitude and time course.

(B) Bath application of Cs⁺ (1 mM) hyperpolarized the neuron by ~5 mV (data not shown) and progressively shortened the spindle wave refractory period until the network was continuously oscillating. Expansion of the intracellular recording illustrates that the barrages of IPSPs arriving in the thalamocortical cell are similar in frequency to control. Expansion of two rebound Ca²⁺ spikes illustrates their amplitude–time course in Cs⁺.

(C) This effect is reversible upon washout of Cs⁺.

resulted in a hyperpolarization of thalamocortical cells of 2 mV–10 mV, as reported previously (McCormick and Pape, 1990a). Comparison of the repetitive IPSPs arriving in thalamocortical cells during Cs⁺ application with those observed in normal bathing medium revealed that the IPSPs were of similar amplitude and frequency (Figures 7A and 7B, middle traces). In addition, rebound low-threshold Ca²⁺ spikes during the spindle oscillations were also similar between these two conditions. Examination of the response of the neuron to hyperpolarizing current pulses before and after application of Cs⁺ revealed that the depolarizing sag representative of activation of I_h was progressively blocked in parallel with the block of the spindle wave refractory period (data not shown).

Discussion

During slow-wave sleep and generalized epileptic seizures, and perhaps during sensory processing, synchronized neuronal activity occurs throughout thalamic and cortical systems (Steriade and Deschênes, 1984; Niedermeyer, 1990; Steriade et al., 1993; Niedermeyer and Lopes da Silva, 1993; Steriade et al., 1994; Singer and Gray, 1995). Spindle waves are synchronized 7 Hz–14 Hz oscillations that are most prominent during the early stages of sleep (Steriade and Deschênes, 1984). Spindle waves are generated through an interaction between thalamic reticular/PGN and thalamocortical neurons

such that the generation of a burst of action potentials in one or more thalamic reticular/PGN cells initiates an IPSP in recipient thalamocortical cells. This IPSP generates a rebound low-threshold Ca²⁺ spike and burst of action potentials in a subpopulation of these thalamocortical cells, which then reexcites the thalamic reticular neurons (Steriade et al., 1993; von Krosigk et al., 1993; Bal et al., 1995a, 1995b). In this manner, spindle waves are generated as a simple reciprocal loop between thalamic reticular and thalamocortical neurons.

The waxing of spindle waves is associated with a progressive recruitment of neurons into the synchronized network oscillation, with individual neurons receiving IPSPs that steadily increase in amplitude during approximately the first half of the oscillation (Bal et al., 1995a, 1995b; Kim et al., 1995). This progressive recruitment of neurons into the synchronized oscillation can appear as a propagation of the spindle wave through the tissue (Andersen and Andersson, 1968; Kim et al., 1995). In addition to the waxing of the spindle wave, these oscillations also wane in that after approximately halfway through the total duration of the spindle wave, fewer and fewer neurons discharge and each neuron discharges less and less intensely until the oscillation ceases in the local tissue (although it may have propagated to another portion of the network).

The waning of spindle waves is followed by a relative refractory period during which the threshold for the initiation of another spindle wave is markedly increased

(Kim et al., 1995). For example, extracellular electrical stimulation, or depolarization of a single PGN neuron, can initiate a spindle wave that then propagates throughout the thalamic slice *in vitro* away from the point of initiation. Following the generation of a spindle wave, application of the extracellular stimulus does not generate a full spindle wave or the propagation of such. As the time since the generation of the last spindle wave lengthens, the ability of the network to generate another spindle wave recovers, such that after a period of ~ 10 s, an additional spindle wave may be generated that then propagates throughout the slice (Kim et al., 1995).

Together, the properties of waxing, waning, and refractory period characterize the regular recurrence of spindle waves at approximately one every 5 s–20 s, both *in vivo* and *in vitro* (Steriade and Deschênes, 1984; Bal et al., 1995a, 1995b; Kim et al., 1995). Block of GABA_A receptors in the spontaneously spindling thalamic slice results in a transformation of spindle waves into paroxysmal events in which each thalamocortical and PGN neuron discharge strongly in a synchronized 2 Hz–4 Hz oscillation (von Krosigk et al., 1993; Bal et al., 1995a, 1995b) that is similar to the activity generated by these cells during generalized spike-and-wave, or absence, seizures (reviewed by Avoli et al., 1990). These synchronized oscillations exhibit the same network properties as spindle waves, except that the refractory period between oscillations is longer (Kim et al., 1995).

Recent electrophysiological data suggest that the progressive failure and refractory period for network oscillations may result from the properties of single thalamocortical cells. Thalamic relay neurons have the ability to generate rhythmic bursts of action potentials through the interaction of the low-threshold Ca²⁺ current and the h-current (McCormick and Pape, 1990a; Soltesz et al., 1991). This intrinsic oscillation typically occurs in the delta frequency range (2 Hz–4 Hz) and can exhibit waxing and waning in that the oscillation progressively increases and then decreases in amplitude, even without the generation of action potentials. Each waxing and waning cluster of rhythmic burst firing is separated from the others by ~ 5 s–20 s, during which a slow afterdepolarization similar to that studied here occurs (Leresche et al., 1991; Soltesz et al., 1991). This result indicates that single thalamocortical neurons possess the ability to generate, through intrinsic ionic mechanisms, the interspindle period of one waxing and waning oscillation approximately once every 5 s–20 s.

The cellular mechanisms for the generation of this waxing and waning oscillation in single thalamic cells was suggested by the observation that the enhancement of the hyperpolarization-activated cation current I_h through the application of various neurotransmitters can decrease the ability of single thalamocortical neurons to rhythmically oscillate (McCormick and Pape, 1990b). The enhancement of I_h results in a small depolarization of the membrane potential and a decrease in apparent input conductance of thalamocortical neurons (McCormick and Pape, 1990b). Together, these two effects decrease the propensity of thalamocortical cells to oscillate through the inactivation of the low-threshold Ca²⁺ current and the reduction of the hyperpolarizations that occur in between each Ca²⁺ spike (thereby reducing

the degree to which the inactivation of the low-threshold Ca²⁺ current is removed by the hyperpolarization).

Computational models of single thalamic relay neurons can replicate the generation of waxing and waning intrinsic oscillations if either the slow activation and deactivation kinetics of I_h are carefully accounted for (Destexhe et al., 1993a) or the voltage dependence of I_h activation is considered to be sensitive to [Ca²⁺]_i (Destexhe et al., 1993b; 1996). In addition, computational models of networks of interacting thalamocortical and PGN neurons also reveal that persistent activation of I_h is capable of generating an afterdepolarization and spindle wave refractory period similar to that observed in real neurons (Destexhe et al., 1993b; 1996).

Here, we demonstrate that the spontaneous cessation of synchronized thalamocortical oscillations is generated at least in part through the progressive activation of the hyperpolarization-activated cation current I_h. This persistent activation of I_h results in a relative refractory period during which the propensity to generate synchronized oscillations is markedly reduced. Each spindle wave or bicuculline-induced paroxysmal oscillation is followed by a 1 mV–4 mV afterdepolarization, the duration of which matches the duration of the refractory period (5 s–20 s). Intracellular injection of repetitive hyperpolarizing current pulses, which activate I_h, also resulted in the same afterdepolarization, and spindle waves or bicuculline-induced oscillations that occurred during this induced afterdepolarization were associated with a marked decrease in the amplitude of the rebound low-threshold Ca²⁺ spikes. In addition, the ability of a burst of action potentials in a single PGN neuron to generate rebound burst firing in thalamocortical cells is markedly depressed immediately following the generation of a spindle wave, and this depression recovers with the same time course as the decrease in the afterdepolarization.

Although the afterdepolarization is relatively small (1 mV–4 mV), intracellular injection of d.c. in thalamocortical cells reveals that it is large enough to reduce the amplitude or suppress the occurrence of rebound low-threshold Ca²⁺ spikes in these neurons (for example, see Figure 2). The selective abolition of the slow afterdepolarization, both those that follow the intracellular injection of hyperpolarizing current pulses as well as those that follow network oscillations, by extracellular application of Cs⁺ indicates that this afterdepolarization is mediated by the persistent activation of I_h. Importantly, the bath or local application of Cs⁺ not only resulted in an abolition of the slow afterdepolarization, but also of the spindle wave refractory period, resulting in synchronized 6 Hz–10 Hz oscillations that occurred continuously without the typical waxing and waning associated with normal spindle waves (Figure 7).

These results indicate that spindle waves and bicuculline-induced slow oscillation is associated with the persistent activation of I_h, which then reduces the responsiveness of these cells to IPSPs by increasing the membrane conductance as well as by depolarizing thalamocortical cells toward the reversal potential for the h-current (approximately –35 mV). Presumably, with each hyperpolarization and rebound burst, more and more I_h is persistently activated, resulting in a progressive increase in the input conductance of the neuron and

depolarization of the membrane potential. We speculate that this progressive activation of I_h results in a progressive decrease in the amplitude of rebound burst firing in thalamocortical neurons, which then results in a decrease in the amplitude of the barrages of EPSPs arriving in the GABAergic PGN neurons. Presumably, this decrease in excitation of PGN neurons is then reflected as a decrease in the action potential discharge of these cells (as a population), resulting in a decrease in the amplitude of the IPSPs initiated in the thalamocortical cell during the next cycle of the oscillation. In this manner, the interaction between PGN and thalamocortical cells that underlies the generation of these synchronized oscillations may progressively fail, leading to the cessation of the network oscillation. Following the cessation of the oscillation, only the persistent activation of I_h remains, resulting in the generation of the afterdepolarization and the relative refractory period.

It is unlikely that the block of the spindle wave refractory period by extracellular application of Cs^+ is due to the block of K^+ currents, since this ion only blocks outward K^+ currents when applied intracellularly, prior investigations have not demonstrated a clear effect of extracellular application of Cs^+ on K^+ currents (McCormick and Pape, 1990a), we did not observe any appreciable effect on the duration of action potentials in thalamocortical cells with the extracellular application of Cs^+ , and the application of Cs^+ resulted in a hyperpolarization of the resting membrane potential, as expected from block of I_h (McCormick and Pape, 1990a).

Although our data argue strongly that I_h is critically involved in the generation of the waning of spindle waves and the generation of the refractory period, it does not rule out the contribution of other factors. For example, intracellular recordings in PGN neurons *in vitro* reveal that these cells progressively hyperpolarize during the generation of spindle waves and this hyperpolarization may be large enough to bring the cell below threshold for generation of low-threshold Ca^{2+} spikes. Previously, we have proposed that this progressive hyperpolarization of PGN neurons may contribute to the generation of the spindle wave refractory period (von Krosigk et al., 1993). However, the general applicability of the hyperpolarization of the GABAergic neurons to the waning of spindle waves is unclear, since available evidence suggests that at least some thalamic reticular neurons progressively depolarize during the generation of spindle waves *in vivo* (Mulle et al., 1986; Steriade et al., 1986). Another mechanism that may be involved in the waning of spindle waves is the presynaptic inhibition of GABA release from thalamic reticular/PGN neurons, since the repetitive activation of IPSPs in the thalamus exhibits this property (von Krosigk and McCormick, 1992, *Soc. Neurosci.*, abstract; Ulrich and Huguenard, 1996). However, presynaptic inhibition of GABA release is mediated by activation of $GABA_B$ receptors (Soltész and Crunelli, 1992; Thompson et al., 1993; Ulrich and Huguenard, 1996), and we have not observed marked effects on the generation of spindle waves or the spindle wave refractory period following the block of $GABA_B$ receptors (von Krosigk et al., 1993; Bal et al., 1995a, 1995b).

Intracellular recordings of thalamocortical cells *in vivo* have revealed a small afterdepolarization following each

spindle wave, although these afterdepolarizations were not specifically mentioned (see Figure 9 in Steriade et al., 1985; see Figure 10 in Deschênes et al., 1984). In other intracellular recordings *in vivo* from thalamocortical neurons, a small and prolonged hyperpolarization following the generation of a spindle wave was sometimes observed (Nunez et al., 1992), and this event was proposed to result from a tonic afterdischarge in thalamic reticular cells. The presence of such a small hyperpolarization does not indicate that the persistent activation of I_h did not occur in these cells, nor does it indicate that I_h did not contribute to the waning of spindle waves. Rather, this result only indicates that the net effect of the inward and outward currents in the recorded thalamocortical cell following the generation of the spindle wave was hyperpolarizing. At any rate, the ability of extracellular application of Cs^+ to completely block the spindle wave refractory period *in vitro* suggests that the above-mentioned additional factors are not sufficient to cause the cessation of spindle waves by themselves.

The cellular mechanisms for the persistent activation of I_h during and following repetitive hyperpolarization have not been determined yet. Previous investigations in cardiac cells suggest that the voltage dependence and maximal conductance of the equivalent hyperpolarization-activated cation conductance may be sensitive to $[Ca^{2+}]_i$ (Hagiwara and Irisawa, 1989), suggesting that the occurrence of repetitive Ca^{2+} spikes during the oscillation may result in the enhancement of I_h . However, our finding that depolarization of the membrane potential may abolish the slow afterdepolarization, presumably through deactivation of I_h , is not consistent with this hypothesis, since $[Ca^{2+}]_i$ would likely remain elevated. Although a Ca^{2+} -dependent shift in the voltage dependence of I_h may have slower kinetics than the actual rise in $[Ca^{2+}]_i$, a more parsimonious explanation is that the persistent activation of I_h is due to a slow rate of deactivation at membrane potentials of -63 mV to -68 mV.

Our results suggest that the persistent activation of the h-current following repetitive hyperpolarization may be a common mechanism by which synchronized oscillations normally terminate. The widespread presence of the h-current in neurons throughout the brain, including the cerebral cortex and hippocampus (Halliwell and Adams, 1982; Spain et al., 1991), suggest that this current may play a similar role in synchronized network activity in these forebrain structures, such as that which occurs during both normal and abnormal forebrain function (Avoli et al., 1990; Steriade et al., 1993). Indeed, it is intriguing to speculate that the spontaneous cessation of generalized absence seizures may occur through the progressive and persistent activation of I_h . If this hypothesis is true, then manipulations that reduce this ionic current should exacerbate these generalized seizures, while manipulations that enhance it may help to prevent them. These possibilities remain to be explored.

Experimental Procedures

Male or female ferrets, from 2 months old to 12 months old, were deeply anesthetized with sodium pentobarbital (30 mg/kg intraperitoneal) and sacrificed by decapitation in accordance with Yale University Medical School guidelines for the use of animals in research.

Sagittal slices (400 μm thick) were prepared on a vibratome and maintained in an interface chamber at 34°C – 35°C . The perfusion medium contained the following: 126 mM NaCl; 2.5 mM KCl; 1.2 mM–2.0 mM MgSO_4 ; 1.25 mM NaH_2PO_4 ; 2 mM CaCl_2 ; 26 mM NaHCO_3 , and 10 mM dextrose. Solutions were aerated with 95% O_2 , 5% CO_2 to pH 7.4. Drugs were applied either locally with the pressure-pulse technique or in the bathing medium. Intracellular recording electrodes contained 1.2 M potassium-acetate and 2% biocytin. During recording, the location of the PGN and each lamina of the LGNd were visible. Cells intracellularly labeled with biocytin were visualized through standard techniques. Activation of neurons in the PGN or interlamina regions with the application of glutamate was achieved with the pressure-pulse technique in which small (1 μl –10 μl) drops of glutamate were extruded from a broken micropipette (3 μm –5 μm tip diameter) through the delivery of a pulse of pressure to the micropipette. The tip of the electrode was placed \sim 50 μm –150 μm into the slice.

The ability of a burst of action potentials in a PGN neuron to initiate a burst of action potentials in thalamocortical neurons was investigated through the intracellular injection of a depolarizing current pulse in a single PGN cell. Intracellular injection of a depolarizing current pulse was used to initiate a low-threshold Ca^{2+} spike and burst of 5–15 action potentials in a single PGN neuron. Often, this burst of action potentials was followed by a return barrage of EPSPs, as described previously (Bal et al., 1995a, 1995b). Subsequently, an extracellular multiple unit electrode was placed just on the surface of the slice and gently moved horizontally until cells were located that rebound burst in response to the activation of the PGN cell. The multiple unit electrode was then lowered into the slice at this recording location and the PGN cell was activated approximately once every 2 s–3 s while spontaneous spindle waves occurred. The peak amplitude of the return barrage of EPSPs and the number of action potentials (as detected by a Schmidt trigger set at $2\times$ noise level and during the window of 100 ms–160 ms after the beginning of the burst of action potentials in the PGN cell) was then counted and grouped into bins according to the time before or after the occurrence of a spontaneous spindle wave. The PGN cells were hyperpolarized to approximately -75 mV to -80 mV to prevent fluctuations in the membrane potential associated with spindle wave generation (Bal et al., 1995b).

Acknowledgments

We thank Uhnoh Kim and Mavi Sanchez-Vives for their contribution and discussion of this paper. This research was supported by the National Institutes of Health and the Klingenstein Fund. The original data for each figure and a program for viewing and analyzing it are available at the web site <http://info.med.yale.edu/neurobio/mccormick/mccormick>. Correspondence should be addressed to D. A. M.

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Received April 2, 1996; revised June 24, 1996.

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