

Periodicity of Thalamic Spindle Waves Is Abolished by ZD7288, a Blocker of I_h

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Lüthi, Anita, Thierry Bal, and David A. McCormick. Periodicity of thalamic spindle waves is abolished by ZD7288, a blocker of I_h . *J. Neurophysiol.* 79: 3284–3289, 1998. The actions of the novel bradycardiac agent ZD7288 [4-(*N*-ethyl-*N*-phenylamino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride] were investigated on the hyperpolarization-activated cation current I_h and on network activity in spontaneously spindling ferret lateral geniculate (LGNd) slices in vitro using intracellular recording techniques. In voltage-clamp recordings, local application of ZD7288 (1 mM in micropipette) resulted in a complete block of I_h , whereas in current-clamp recordings, application of this agent resulted in an abolition of the depolarizing sag activated by hyperpolarization and decreased the frequency of intrinsic δ -oscillations for which I_h acts as a pacemaker current. In addition, block of I_h with ZD7288 resulted in an abolition of the afterdepolarization (ADP) that follows repetitive hyperpolarization and rebound burst firing as well as that occurring in between spindle waves. The block of the ADP was associated with a block of the spindle wave refractory period such that continuous 6- to 10-Hz oscillations were generated throughout the network. These findings give further support to the hypothesis that I_h is critically involved in the generation of slow rhythmicity in synchronized thalamic activity.

INTRODUCTION

A prominent feature of thalamocortical networks is the generation of various patterns of normal and pathological synchronized network oscillations (Avoli et al. 1990; McCormick and Bal 1997; Niedermeyer 1990; Steriade et al. 1993a). Many of these network oscillations contain low-frequency components (e.g., 0.1–1 Hz) in which synchronized neuronal activity is interspersed with periods of quiescence or less synchronized activity. For example, spindle waves appear as a 1- to 3-s period of 6- to 14-Hz synchronized oscillatory activity that recurs approximately once every 5–20 s (Contreras et al. 1997; Steriade and Deschênes 1984; Steriade et al. 1993a). In between spindle waves, thalamocortical networks exhibit a relative refractory period, the strength of which depends on the period of time that has passed since the last generation of a spindle wave (Contreras et al. 1997; Kim et al. 1995). Additional examples of periodicities on the order of seconds to tens of seconds in synchronized cortical or thalamocortical activity are found in the recurring pattern of the cortical slow rhythm (Steriade et al. 1993b), the cyclic alternating pattern of non-rapid eye movement sleep (Terzano et al. 1985), and the periodicity of spike-and-wave seizures in some animal models of absence epilepsy (Jandó et al. 1995; Kostopoulos et al. 1981).

Recent in vitro experiments have revealed possible mech-

anisms underlying the slow (0.05–0.2 Hz) recurrence of spindle waves (Bal and McCormick 1996). Spindle waves are generated as a circuitous interaction between thalamocortical neurons and the inhibitory GABAergic cells of the perigeniculate/thalamic reticular nuclei (Bal et al. 1995a,b; Steriade et al. 1993a). The arrival of repetitive inhibitory postsynaptic potentials (IPSPs) concomitantly with increases in intracellular Ca^{2+} due to rebound Ca^{2+} spikes during spindle waves leads to activation and upregulation of the hyperpolarization-activated mixed cationic current known as I_h (Bal and McCormick 1996; Lüthi and McCormick 1998; McCormick and Pape 1990; Pape 1996). Persistent activation of I_h depolarizes thalamocortical neurons to such an extent that they no longer respond to these IPSPs with the generation of rebound Ca^{2+} spikes, thus resulting in the decrement or “waning” of spindle waves (Bal and McCormick 1996; Lüthi and McCormick 1998). Thus the rhythmicity of spindle waves and the refractory period may be generated in large part via periodic activation of I_h .

Support for this hypothesis has been obtained from experiments blocking I_h with extracellular application of Cs^+ (Bal and McCormick 1996), as well as enhancing of I_h via serotonin and norepinephrine (Lee and McCormick 1996). Thus the block of I_h with application of low concentrations of Cs^+ results in an abolition of the slow periodicities in spindle wave generation such that spindle waves are generated in a continuous manner and enhancement of I_h with serotonin or norepinephrine results in the abolition of spindle waves through the depolarization of thalamocortical neurons.

The drug ZD7288 is a bradycardiac agent with a selectivity for the cardiac equivalent of I_h , the pacemaker current I_f (BoSmith et al. 1993). This drug also blocks I_h in guinea pig substantia nigra neurons, rat hippocampal CA1 cells, and cat ventrobasal thalamocortical neurons with minor effects on other membrane properties (Gasparini and di Francesco 1997; Harris and Constanti 1995; Williams et al. 1997). Here we reinvestigated the functional properties of I_h in thalamocortical neurons and its role in spindle wave generation by blocking this current with ZD7288.

METHODS

Male or female ferrets, ~2 mo old, were deeply anesthetized with pentobarbital sodium (30 mg/kg ip) and killed by decapitation in accordance with Yale University Medical School guidelines for the use of animals in research. Sagittal slices (350–400 μ m thick) were prepared on a vibratome and maintained in an interface chamber at 34–35°C. The perfusion medium contained the follow-

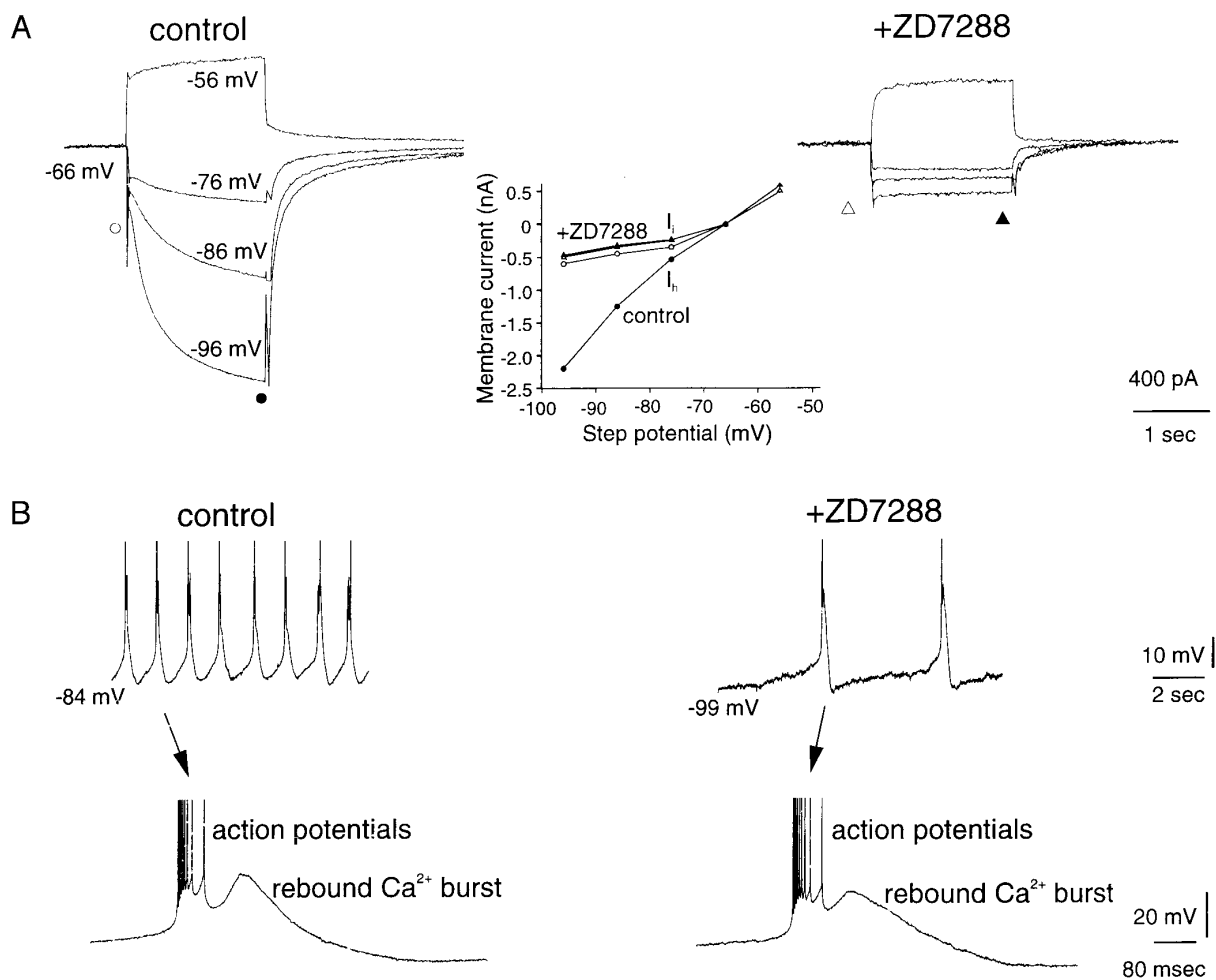


FIG. 1. Local application of ZD7288 (1 mM in micropipette) reduces I_h in thalamocortical cells. *A*: I_h -current responses to 1.8-s hyperpolarizing voltage steps in a cell held at -66 mV under control conditions (*left*) and in the presence of ZD7288 (*right*). Voltages corresponding to each current trace are indicated. Inward currents due to activation of I_h were completely absent in the presence of ZD7288, whereas depolarization-induced outward currents were not reduced. *Inset*: plot of the current responses, measured at the beginning of the voltage step after the decay of the capacitive transients (\circ and \triangle), as well as at the end of the hyperpolarizing step (\bullet and \blacktriangle). Large, unclamped inward currents were evoked upon stepping back to -66 mV due to activation of low-threshold Ca^{2+} currents. These appear truncated in the figure. *B*: thalamocortical cell that generated intrinsic oscillations at a frequency of ~ 2 Hz. In the presence of ZD7288, the cell hyperpolarized and spontaneous discharges occurred at a frequency below ~ 0.2 Hz. Similar reductions in oscillatory activity were observed at all values of membrane potentials, as assessed with various DC injections (not shown). Traces below depict 1 burst discharge for each condition.

ing (in mM): 126 NaCl, 2.5 KCl, 1.25 NaH_2PO_4 , 26 NaHCO_3 , 2 CaCl_2 , 1.2 MgSO_4 , and 10 dextrose. Solutions were aerated with 95% O_2 -5% CO_2 to pH 7.4. Drugs were applied locally (within 0.1–0.2 mm from the cell) with the pressure-pulse technique in which small (1–10 μl) drops of drug solution were extruded from a broken micropipette (3–5 μm tip diameter). To study the effects of ZD7288 on network activity, this drug was applied more remote (0.2–0.4 mm) from the recorded cell to prevent extensive local hyperpolarization. Intracellular recording electrodes contained 2 M potassium acetate, adjusted to pH 7.2–7.3. Intracellular recordings were performed with micropipettes formed on a Sutter Instruments P-80/PC micropipette puller from medium-walled glass (IB100F, World Precision Instruments) and beveled on a Sutter Instruments beveler. Electrode resistances ranged between 80 and 120 $\text{M}\Omega$ for current-clamp recordings and between 50 and 90 $\text{M}\Omega$ for voltage-clamp recordings. Voltage clamp was performed by the discontinuous single-electrode voltage-clamp technique using an Axoclamp-2A amplifier (Axon Instruments) in which the output of the head-

stage was continuously monitored in order to ensure adequate settling time between samples (switching frequency 1.5–2.5 kHz). Only those cells that exhibited stable resting membrane potentials of between -60 and -70 mV and input resistances in excess of 50 $\text{M}\Omega$ were included for analysis. ZD7288 was obtained from Tocris Cookson. All other chemicals were obtained from Sigma.

RESULTS

To establish the effectiveness of ZD7288 in blocking I_h in thalamocortical cells, neurons were voltage clamped to membrane potentials of -49 to -66 mV and repetitively stepped to increasingly more negative membrane potentials covering the full activation range of I_h . Activation of I_h was characterized by a slowly developing inward current in response to negative voltage steps that reached maximal levels around -100 mV, as demonstrated previously (Fig. 1A)

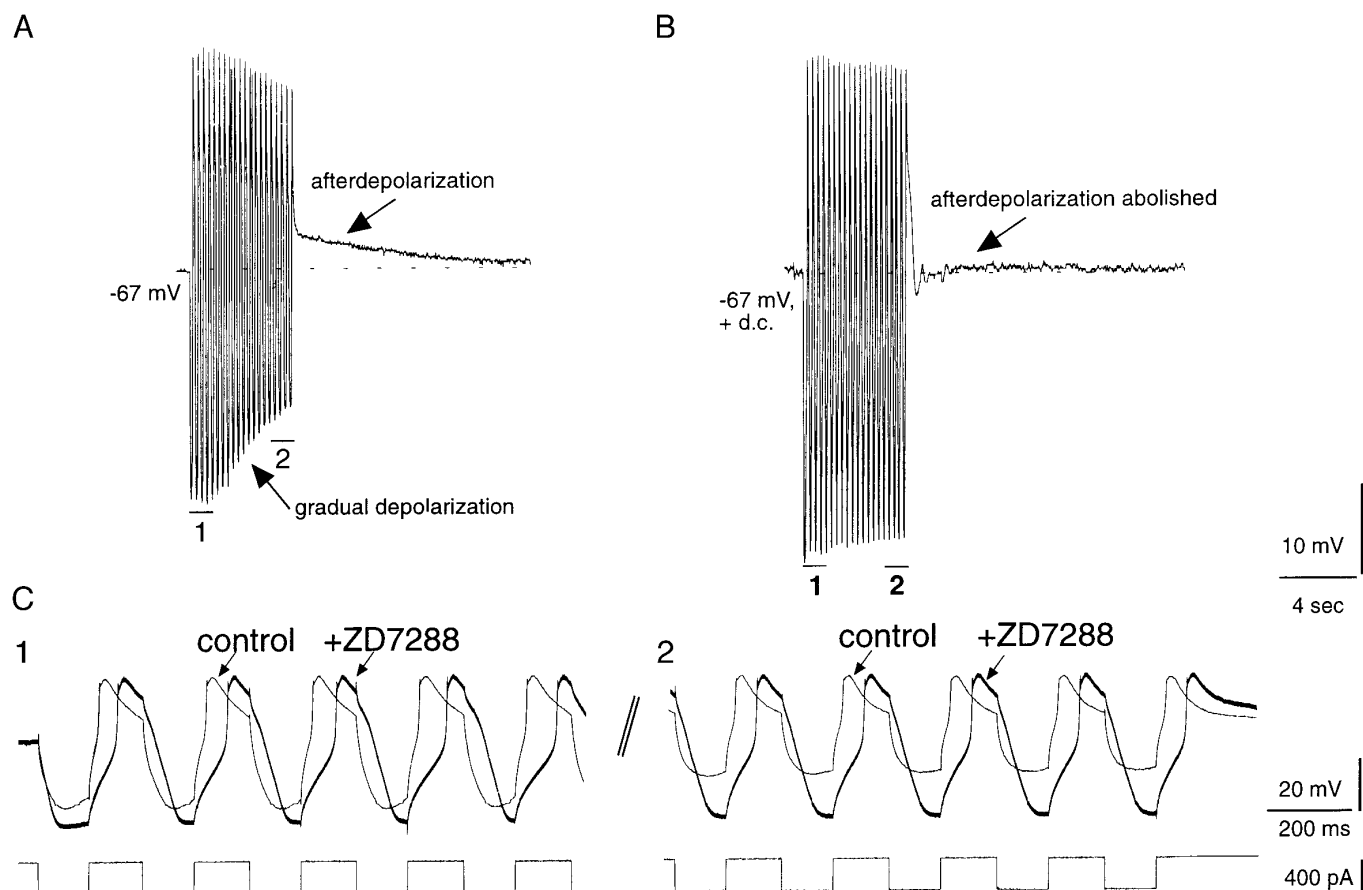


FIG. 2. ZD7288 blocks the afterdepolarization (ADP) that follows repetitive hyperpolarization and rebound low-threshold Ca^{2+} spikes. Tetrodotoxin ($10 \mu\text{M}$, local application) was present throughout the experiment. *A*: thalamocortical cell injected with 20 hyperpolarizing current pulses (each -400 pA , 120 ms in duration, frequency 4 Hz). This resulted in a sustained ADP decaying in $\sim 12 \text{ s}$. During the repetitive pulses, the cell displayed a gradual depolarization. Input resistance under control conditions was $\sim 90 \text{ M}\Omega$. *B*: both the ADP and the gradual depolarization during the hyperpolarizing pulses were abolished in the presence of ZD7288. Input resistance was increased to $115 \text{ M}\Omega$. *C*: membrane potential responses to the hyperpolarizing current injections are presented at an expanded time scale (control: thin lines; ZD7288: thick lines). *C1*: responses to the initial 5 pulses. *C2*: responses to the last 5 pulses. The control responses gradually diminished in size (compare *C1* and *C2*), whereas the responses in ZD7288 did not change in amplitude.

(McCormick and Pape 1990). Local application of ZD7288 (1 mM in micropipette) to the surface of the slice induced a progressive reduction in the time-dependent inward currents with a blocking effect being fully developed after 6–18 min (Fig. 1A, $n = 10$). A plot of the current-voltage curve demonstrated that the inward current due to activation of I_h was fully blocked in the presence of ZD7288, with little, if any, effect on passive current, measured at the onset of the voltage step after the decay of the capacitive transients (Fig. 1A, *inset*). Thus, in agreement with studies of cardiac cells and central neurons (BoSmith et al. 1993; Gasparini and di Francesco 1997; Harris and Constanti 1995; Williams et al. 1997), ZD7288 acts as a selective blocker of I_h in thalamocortical cells at potentials below approximately -60 mV . The blocking effect of ZD7288 did not recover after 1 h following start of wash out, confirming the irreversible action of this drug reported earlier (Gasparini and di Francesco 1997; Harris and Constanti 1995; Williams et al. 1997).

Thalamocortical cells have a tendency to intrinsically oscillate at frequencies between 1 and 2 Hz, generating so-called δ -oscillations (McCormick and Pape 1990; Soltesz et

al. 1991). These oscillations are generated by a cyclical interaction between the low-threshold Ca^{2+} current I_T and the hyperpolarization-activated cation current I_h . Local application of ZD7288 onto δ -oscillating neurons resulted in a 10- to 20-mV membrane hyperpolarization and a progressive lengthening of the interburst interval (Fig. 1B, $n = 7$), followed, in general, by a complete and irreversible cessation of activity (not shown). ZD7288 did not have marked effects on the generation of action potentials or low-threshold Ca^{2+} spikes (Fig. 1B, expanded traces).

Intracellular injection of repetitive hyperpolarizing constant current pulses (5–20 pulses, 2–7 Hz, 120 ms), mimicking the arrival of inhibitory input during spindle oscillations, resulted in a gradual reduction in the electrotonic response to each pulse (Fig. 2A, gradual depolarization) as well as the generation of a 10- to 15-s duration afterdepolarization (ADP; Fig. 2A, afterdepolarization), as reported previously (Bal and McCormick 1996). This ADP was recently shown to result from voltage- and Ca^{2+} -mediated upregulation of I_h (Lüthi and McCormick 1998). Application of ZD7288 led to a complete block of both the ADP and the

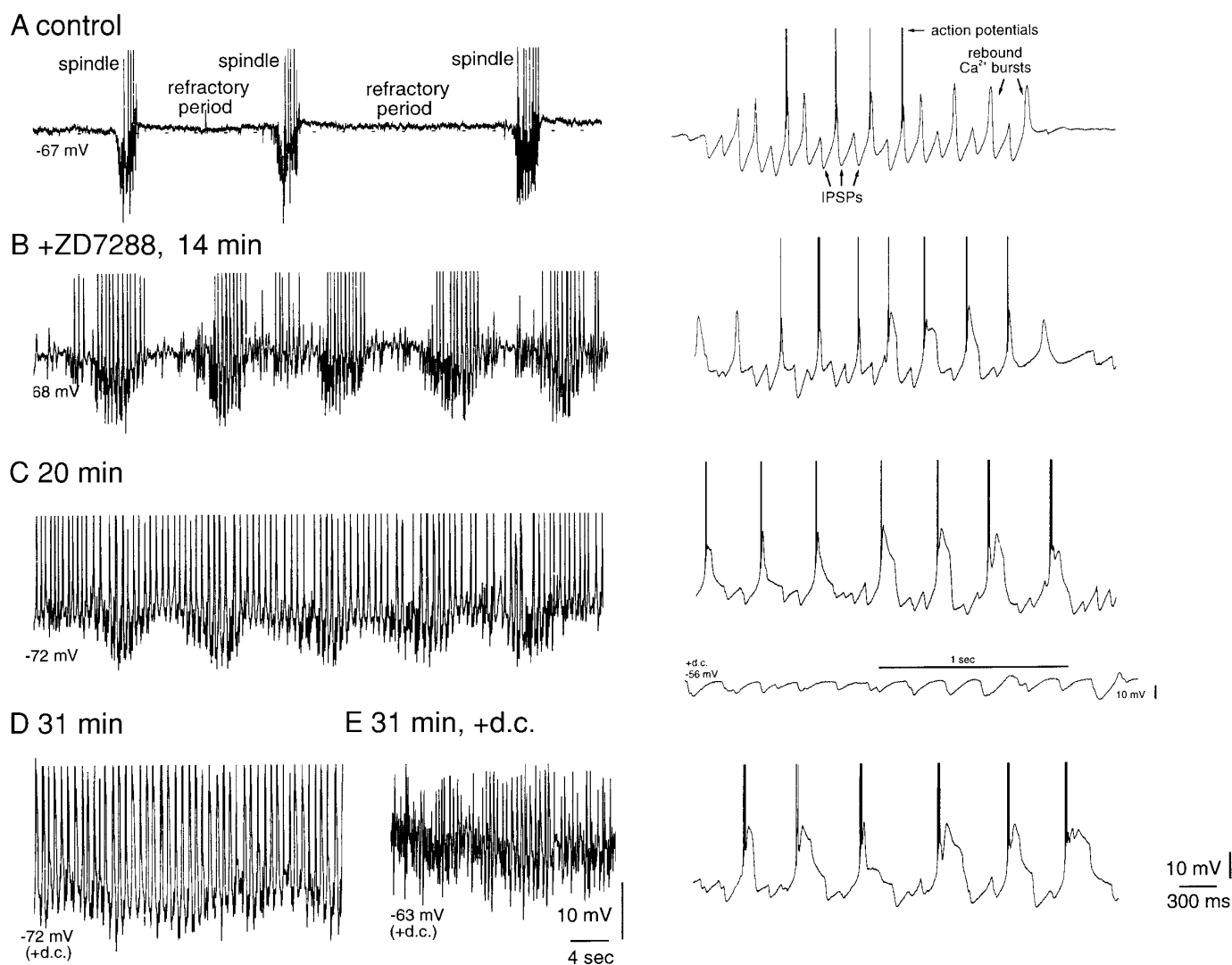


FIG. 3. ZD7288 abolishes the periodicity of spindle waves in vitro. Expanded portions of each trace on the *left* are presented on the *right* (for A–D). *A*: recording from a thalamocortical cell participating in spontaneous spindle waves and displaying an alternating sequence of spindles and refractory periods. Each refractory period was associated with a small ADP. *B*: application of ZD7288 to the cell initially resulted in a lengthening and shortening of oscillatory and silent periods, respectively, and an appearance of small inhibitory postsynaptic potentials (IPSPs) during the refractory period. *C*: further wash in of ZD7288 led to a disappearance of silent phases, but some degree of periodicity remained, as apparent by inspecting the envelopes of membrane potential. *D*: eventually, spindles occurred continuously, and no periodicity remained. *Inset* (boxed): continuous occurrence of IPSPs, when the cell was depolarized with DC injection to block rebound Ca^{2+} spikes. *E*: depolarization of the cell by DC injection to control membrane potential levels also shows that the oscillatory activity occurs continuously. Action potentials are truncated in the figure.

gradual depolarization (Fig. 2, *B* and *C*, $n = 6$). Furthermore, the sag depolarization of thalamocortical cells during the repetitive current injections was also abolished by ZD7288 (Fig. 2*C*), demonstrating that these effects on membrane potential were entirely due to the progressive activation and Ca^{2+} -mediated upregulation of I_h (Bal and McCormick 1996; Lüthi and McCormick 1998).

Previously, we have suggested that the spindle wave refractory period is generated in large part through the persistent activation of I_h in thalamocortical cells (Bal and McCormick 1996; Lüthi and McCormick 1998). To test this hypothesis, we locally applied ZD7288 to thalamocortical neurons that were actively participating in the generation of spindle waves (Fig. 3*A*, $n = 7$). Recordings of single cells

were used as a probe to assay network activity in the slice through monitoring the pattern of synaptic potentials arriving in impaled cells. Application of 1–5 picodrops of ZD7288 (1 mM in micropipette) onto the surface of the slice in the A-laminae (200–400 μm from the recorded cell) to block I_h in cells participating in spindle activity induced a gradual increase in the duration of the spindle waves and a shortening of the refractory period (Fig. 3). Approximately 10–20 min after the application of ZD7288, the refractory period between spindle waves was completely abolished, but the oscillations still exhibited slow periodicities indicating the presence of waxing and waning phases of oscillations (Fig. 3, *B* and *C*). Eventually, all signs of periodicity were absent (Fig. 3, *D* and *E*), but cells continued to receive IPSPs in

the frequency range of spindle oscillations (7–14 Hz; Fig. 3D, inset), showing that the network remained functionally intact but now displayed continuous oscillations.

DISCUSSION

Slow periodicities on the time scale of seconds in neuronal oscillations in thalamocortical systems have been repeatedly demonstrated from the level of single cells (Leresche et al. 1991; Soltesz et al. 1991) to small networks in vitro (Bal and McCormick 1996), to intact thalamocortical interactions in vivo (Contreras et al. 1997; Steriade and Deschênes 1984; Steriade et al. 1993a) and finally to the electroencephalogram in humans and animals (Achermann and Borbély 1997; Avoli et al. 1990; Jandó et al. 1995; Steriade et al. 1993a,b). In the case of spindle waves, these slow periodicities have been suggested to result from the synchronization and desynchronization of thalamocortical networks (Andersen and Andersson 1968; Contreras and Steriade 1996; Kim et al. 1995), the hyperpolarization of GABAergic neurons in the perigeniculate and thalamic reticular nuclei (Kim et al. 1996; von Krosigk et al. 1993), and the activation and deactivation of the hyperpolarization-activated cation current I_h (Bal and McCormick 1996). The interval in between spindle waves is associated in thalamocortical cells with a small ADP that is sufficiently large to decrease the effectiveness of evoked IPSPs to generate rebound low-threshold Ca^{2+} spikes, and therefore may disrupt the ability of the network to generate spindle waves (Bal and McCormick 1996). Extracellular application of Cs^+ not only blocked this ADP, but also abolished the spindle wave refractory period, leading to continuous 6- to 10-Hz oscillations in the network.

Although these effects of Cs^+ were concluded to result from the block of I_h , it is also possible that they may have resulted from the disruption of other ionic currents. Cs^+ blocks K^+ -selective hyperpolarization-activated currents in a number of central neurons (Constanti and Galvan 1983; Nisenbaum and Wilson 1995; Uchimura et al. 1989; Williams et al. 1988; Womble and Moises 1993), and these currents are expressed in thalamic ventrobasal neurons (Williams et al. 1997). Furthermore, extracellular Cs^+ blocks Na^+ -dependent K^+ channels (Koh et al. 1994), and more prolonged exposure interferes with K^+ homeostasis in glial cells (Janigro et al. 1997). Although the expression of Na^+ -dependent K^+ channels has not yet been verified in thalamocortical cells, evidence has been obtained that Na^+ -dependent K^+ -currents are present in perigeniculate neurons and that they may contribute to the slow periodicities of spindle wave generation (Kim et al. 1996). Therefore, although the most parsimonious explanation of the effects of extracellular Cs^+ on spindle wave generation is that they are due to block of I_h , this is not the only possible interpretation.

In the present report, we demonstrate that the bradycardiac agent ZD7288 specifically blocked I_h , decreased the frequency of intrinsic δ -oscillations, fully reduced the ADP following repetitive hyperpolarization and rebound Ca^{2+} spikes, and also abolished the spindle wave refractory period. Therefore ZD7288 serves as a useful tool in studying the function of hyperpolarization-activated cation currents, but it has the potential disadvantage of slow onset and irreversibility of action, compared with the rapid and reversible

effects of Cs^+ . The present data strongly support the hypothesis that the refractory period of spindle waves in vitro is generated through the upregulation of I_h and that this is an event necessary to sustain the periodicity of these synchronized thalamic oscillations.

Previous investigations have proposed that spike-and-wave seizures in at least some animal models of absence seizures in children are generated through cellular mechanisms that share a number of common features to those involved in the generation of spindle waves (see Avoli et al. 1983; Buzsáki 1991; Steriade et al. 1993a). An interesting hypothesis is that I_h also plays an important role in the spontaneous cessation of this form of generalized epileptic seizures. This may be tested by examining the effects of intracerebral administration of ZD7288 and/or agents that enhance I_h through the activation of adenylyl cyclase (e.g., Lee and McCormick 1996) on the duration and periodicity of these seizures.

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