

Functional and Ionic Properties of a Slow Afterhyperpolarization in Ferret Perigeniculate Neurons In Vitro

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Kim, Uhnoh and David A. McCormick. Functional and ionic properties of a slow afterhyperpolarization in ferret perigeniculate neurons in vitro. *J. Neurophysiol.* 80: 1222–1235, 1998. Intracellular recordings from spontaneously spindling GABAergic neurons of the ferret perigeniculate nucleus in vitro revealed a fast afterhyperpolarization after each action potential, a medium-duration afterhyperpolarization after each low-threshold Ca^{2+} spike, and a slow afterhyperpolarization after the cessation of spindle waves. The slow afterhyperpolarization was associated with an increase in membrane conductance, and the reversal potential was sensitive to extracellular $[\text{K}^+]_o$, indicating that it is mediated at least in part by the activation of a K^+ conductance. However, the block of Ca^{2+} channels did not block the slow afterhyperpolarization, whereas the block of Na^+ channels did block this event, even after the generation of repetitive Ca^{2+} spikes, indicating that it is mediated by a Na^+ -activated K^+ current. Application of apamin reduced the afterhyperpolarization and enhanced a plateau potential after each low-threshold Ca^{2+} spike. This plateau potential could result in a prolonged depolarization of perigeniculate neurons, even before the application of apamin, resulting in the generation of tonic discharge. The plateau potential was blocked by the local application of tetrodotoxin, indicating that it is mediated by a persistent Na^+ current. The activation and interaction of these slowly developing and persistent currents contributes significantly to low-frequency components of spindle wave generation. In particular, we suggest that the activation of the slow afterhyperpolarization may contribute to the generation of the spindle wave refractory period in vitro.

INTRODUCTION

The intrinsic thalamic circuitry that generates the synchronized thalamocortical oscillations of spindle waves is composed of multiple replicas of reciprocal disynaptic loops between excitatory thalamocortical and inhibitory reticular thalamic nucleus (nRt) neurons (Bal et al. 1995a,b; Steriade et al. 1993). The GABAergic neurons of the nRt are innervated by axon collaterals of thalamocortical fibers that course through this nucleus in route to the cerebral cortex. In turn, the nRt neurons topographically innervate thalamocortical cells, thereby completing disynaptic feedback inhibitory circuits. The perigeniculate nucleus (PGN), a visual sector of the nRt, forms a shell of interconnected GABAergic cells that innervate thalamocortical cells in laminae A, A1, and perhaps C of the dorsal lateral geniculate nucleus (LGNd) (Cucchiari et al. 1991; Kim et al. 1997; Uhlich et al. 1991).

Two distinct categories of functional role have been suggested for the inhibition of LGNd thalamocortical cells by

PGN neurons. Examinations of the role of inhibitory components to visual responses in LGNd thalamocortical cells have led to the suggestions that the PGN may contribute significantly to recurrent, lateral, long-range, and binocular forms of inhibitory interaction (Ahlsen et al. 1985; Eysel et al. 1987; Lindström 1982; Lindström and Wróbel 1990; Sillito and Kemp 1983). Examination of the cellular mechanisms of spindle waves, a synchronized sleep rhythm, also revealed a critical role of the PGN in the generation of these oscillations (reviewed in McCormick and Bal 1997; Steriade et al. 1993). Because both visual processing and sleep rhythms are expressed by the same neuronal networks, at some level they must share common mechanisms, and therefore increases in our knowledge of one will necessarily lead to an increase in our understanding of the other.

Spindle waves, a typical synchronized oscillation that originates from the thalamic network, are most prevalent during the early phases of sleep. Recurring at once every 5–20 s, spindle waves take the form of waxing and waning 7–14 Hz oscillations that last from 1 to 3 s. The detailed investigation of cellular mechanisms for the generation of spindle waves employing ferret LGNd slices in vitro revealed that these events are generated through the reciprocal interaction between perigeniculate and thalamocortical neurons. The generation of a burst of action potentials through the activation of a low-threshold Ca^{2+} spike in a perigeniculate neuron results in the inhibition of thalamocortical cells and a rebound low-threshold Ca^{2+} spike owing to removal of inactivation of this current. The subsequent activation of bursts of action potentials in several thalamocortical cells once again excites the perigeniculate neurons to generate additional burst discharges, thereby perpetuating the generation of the spindle wave. The propagation of the spindle wave to neighboring neurons as well as the increase in strength of discharge of the neurons results in the “waxing” portion of the spindle wave (Andersen and Andersson 1968; Kim et al. 1995).

Whereas the initiation and waxing of spindle waves emerge from network interactions through disynaptic loops between LGNd and PGN cells, the activation of intrinsic currents in component neurons kindled from network interactions was proposed to cause the waning and eventual stop of the oscillation. For example, the progressive activation of the hyperpolarization-activated cation current (h current) in LGNd cells by cyclic inhibitory postsynaptic potentials (IPSPs) arising from PGN cells results in a small depolarization of the membrane potential and a shunt in membrane conductance that can subsequently undermine the capacity of incoming IPSPs to activate rebound cal-

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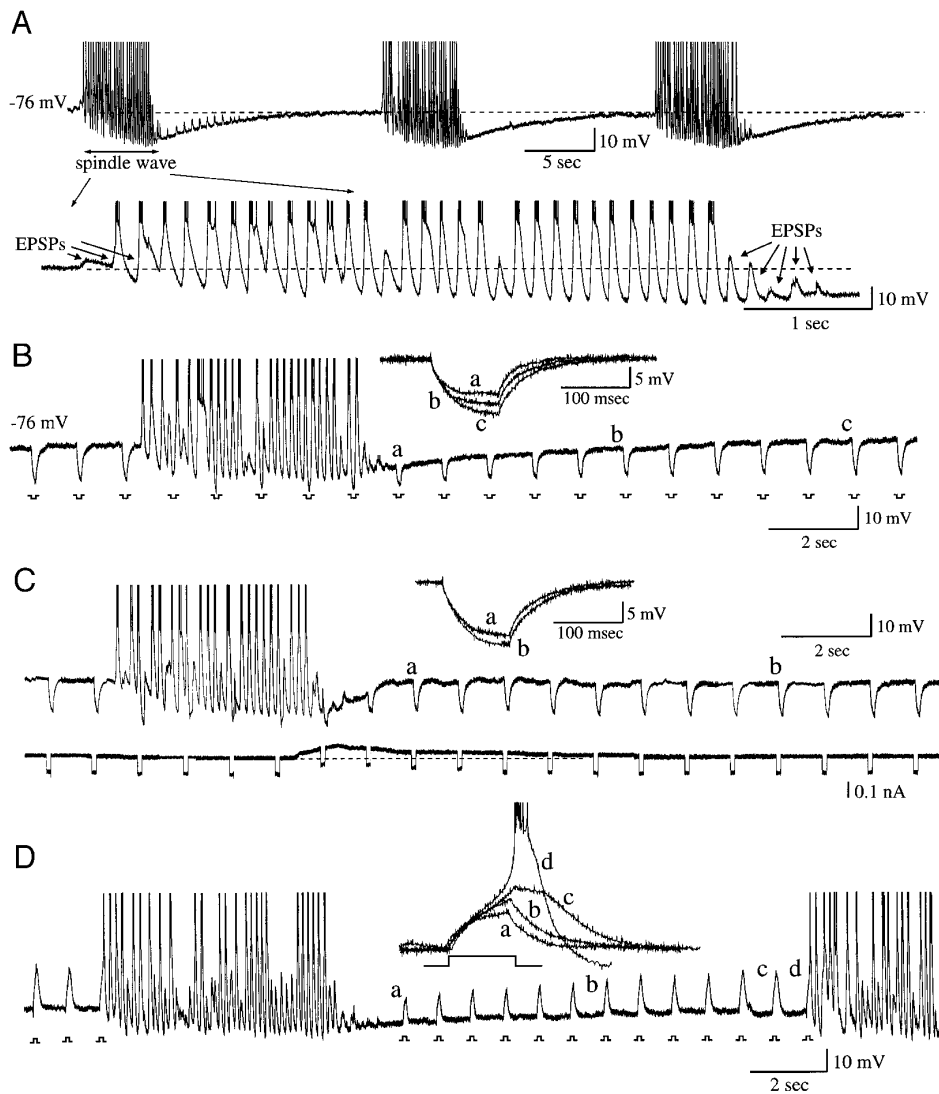


FIG. 1. Oscillatory burst discharges of perigeniculate nucleus (PGN) cells during spindle wave generation are accompanied by a progressive hyperpolarization and are followed by a slow afterhyperpolarization (AHP). Slow AHP occupies most of the interspindle period (*A*). After the 1st spindle wave, there are rhythmic barrages of excitatory postsynaptic potentials (EPSPs) in this neuron, presumably arising from 2- to 4-Hz rhythmic burst firing in thalamocortical cells. *B*: intracellular injection of hyperpolarizing current pulses of 100 ms in duration reveals that the AHP after the spindle wave is associated with a decrease in apparent input resistance. *C*: compensating for the change in membrane potential through the intracellular injection of current revealed the amplitude of the current generated during the AHP as well as the decrease in apparent input resistance. *D*: intracellular injection of depolarizing current pulses once every second reveals that the AHP is associated with a decrease in responsiveness to these inputs and that as the AHP slowly decays, the electrotonic response to these inputs becomes larger and larger until finally the last one initiates a spindle wave.

cium spikes in LGNd cells (Bal and McCormick 1996). The persistent activation of the *h* current results in an afterdepolarization in LGNd cells after each spindle wave and persists throughout the entire refractory period (Bal and McCormick 1996).

Is the persistent activation of the *h* current entirely responsible for the generation of the refractory period? Previously we have demonstrated that during spindle waves *in vitro* PGN cells undergo a progressive hyperpolarization that appears as an afterhyperpolarization, which also persists during the spindle wave refractory period. We suggested that this progressive hyperpolarization may contribute to the waxing and waning of spindle waves *in vitro* (von Krosigk et al. 1993), although the cellular mechanisms for its generation were unknown. Previous investigations of slow afterhyperpolarizations in other cell types, in particular cortical and hippocampal pyramidal cells, sympathetic ganglionic neurons, and thalamocortical cells, have demonstrated at least three different ionic mechanisms for the generation of such afterhyperpolarizations: the activation of Ca^{2+} or Na^{+} -activated K^{+} currents (Foehring et al. 1989; Schwindt et al. 1988, 1989), the activation of an electrogenic ionic pump

(Thompson and Prince 1986), or the deactivation and reactivation of the *h* current (McCormick and Pape 1990).

In the present study, we demonstrate that the slow afterhyperpolarization in PGN GABAergic neurons is generated largely by a Na^{+} -activated K^{+} current and that the activation of this current can have significant effects on the functional responses of perigeniculate neurons and neuronal circuits.

METHODS

For the preparation of slices, 2- to 4-mo-old male or female ferrets were anesthetized deeply with pentobarbital sodium (30 mg/kg) and killed by decapitation. Ferrets were cared for and used in accordance with all appropriate regulatory guidelines. The forebrain was removed rapidly, and the hemispheres were separated with a midline incision. Four-hundred-micrometer-thick sagittal slices were formed on a vibratome (DSK Microslicer; Ted Pella). A modification of the technique developed by Aghajanian and Rasmussen (1989) was used to increase tissue viability. During preparation of slices, the tissue was placed in a solution in which NaCl was replaced with sucrose while maintaining an osmolarity of 307 mOsm. After preparation, slices were placed in an interface-style recording chamber (Fine Sciences Tools) and allowed ≥ 2 h to recover. Intracellular recordings were

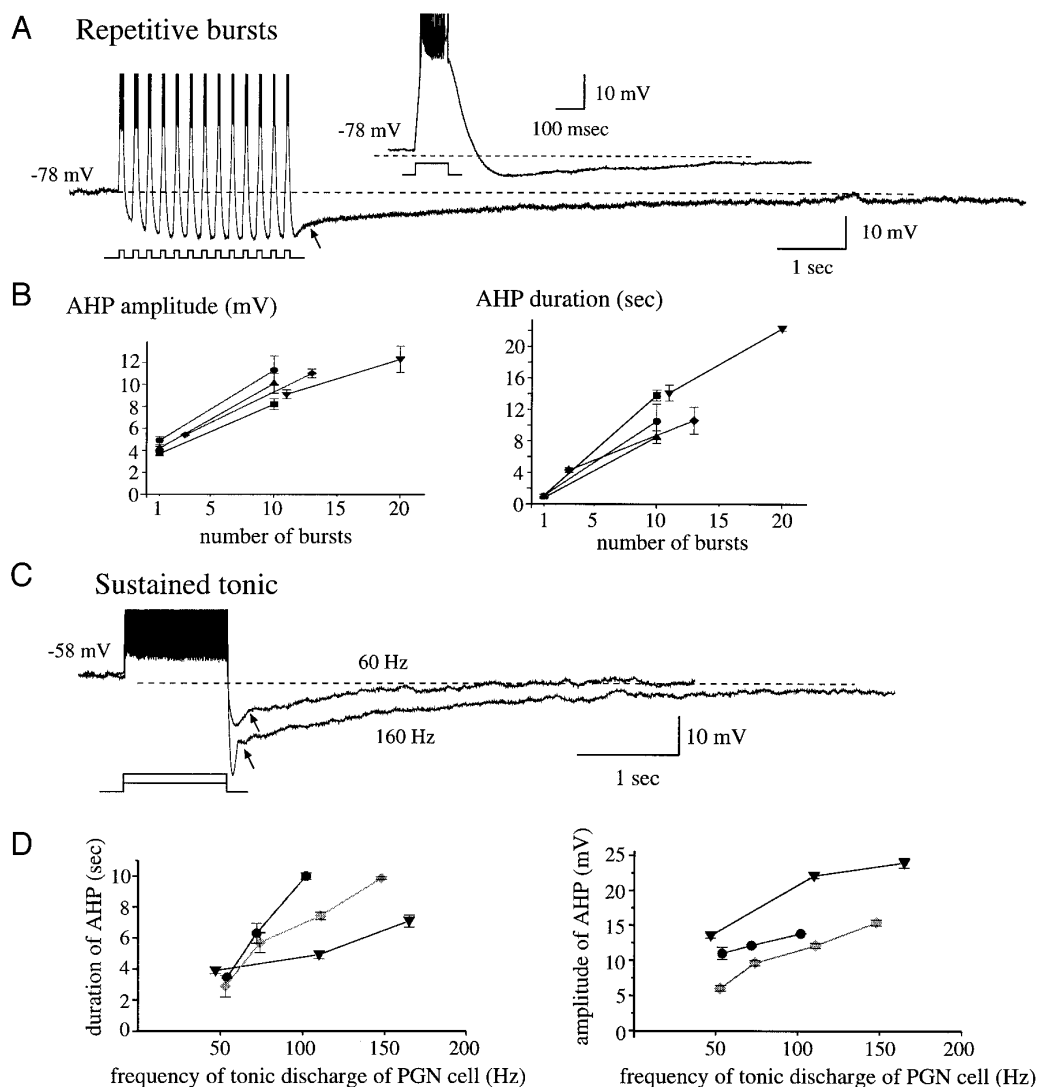


FIG. 2. Progressive hyperpolarization during burst firing and the AHP are both consequences of intrinsic properties. *A*: single burst of action potentials by intracellular current pulse injection is followed by an AHP of ~ 5 mV in amplitude and 1 s in duration. Repetitive induction of burst discharges results in the activation of a pronounced AHP that persists for 5–10 s. AHP decays in 2 phases, indicating early and late components. *B*: amplitude and duration of the late component of the AHP increased with repetitive activation of burst action potentials. Amplitude of the late AHP was measured after rapid decline of the early component (arrow). *C*: slow AHP also can be activated after sustained tonic action potential generation. Early component of the AHP becomes more distinguishable with high frequency of action potential generation. *D*: both the amplitude and duration of the late AHP activated from tonic discharge for 1 s grow with increasing rate of action potential generation. Results from 3 different cells are illustrated.

made from PGN cells in normal bathing medium that contained (in mM): 124 NaCl, 2.5 KCl, 1.2 MgSO₄, 1.25 NaHPO₄, 2 CaCl₂, 26 NaHCO₃, and 10 dextrose and was aerated with 95% O₂-5% CO₂ to a final pH of 7.4.

To increase the viability of the tissue, when geniculate slices were placed in the recording chamber, they were superfused for the first 20 min with an equal mixture in volume of the normal bathing medium and the sucrose-substituted solution. Throughout the remainder of the experiment the slices were bathed in normal medium. Bath temperature was maintained at 34–35°C. After 2 h of recovery, extracellular multiple unit recordings were performed from multiple locations in each slice to determine the prevalence of spontaneous spindling activity.

Intracellular recording electrodes were formed on a Sutter Instruments P-80 micropipette puller from medium-walled glass (WPI, 1BF100) and beveled on a Sutter Instruments beveler. Micropipettes

were filled with either 4 M potassium acetate (KAc) or, in some cases, with 1.5 M KAc and 2% biocytin for intracellular labeling of recorded neurons. Biocytin-filled neurons were visualized through standard avidin-biotin-horseradish peroxidase reaction with diaminobenzidine (Horikawa and Armstrong 1988).

Drugs [tetrodotoxin (TTX), ω -conotoxin, and apamin] were applied locally with the pressure-pulse technique. After the drug-containing microelectrode (1–4 μ m tip diameter) was positioned on the surface of the slice in close proximity (50–100 μ m) to the entry point of the intracellular electrode, a brief pulse of pressure (10–250 ms; 200–350 kPa) was applied to the back of the microelectrode to extrude 1–20 μ l of solution.

When calcium ions in normal bathing medium were replaced with equimolar cobalt ions to block calcium entry, sodium phosphate was omitted from the bathing medium and magnesium sulfate was substituted with magnesium chloride to avoid precipitation.

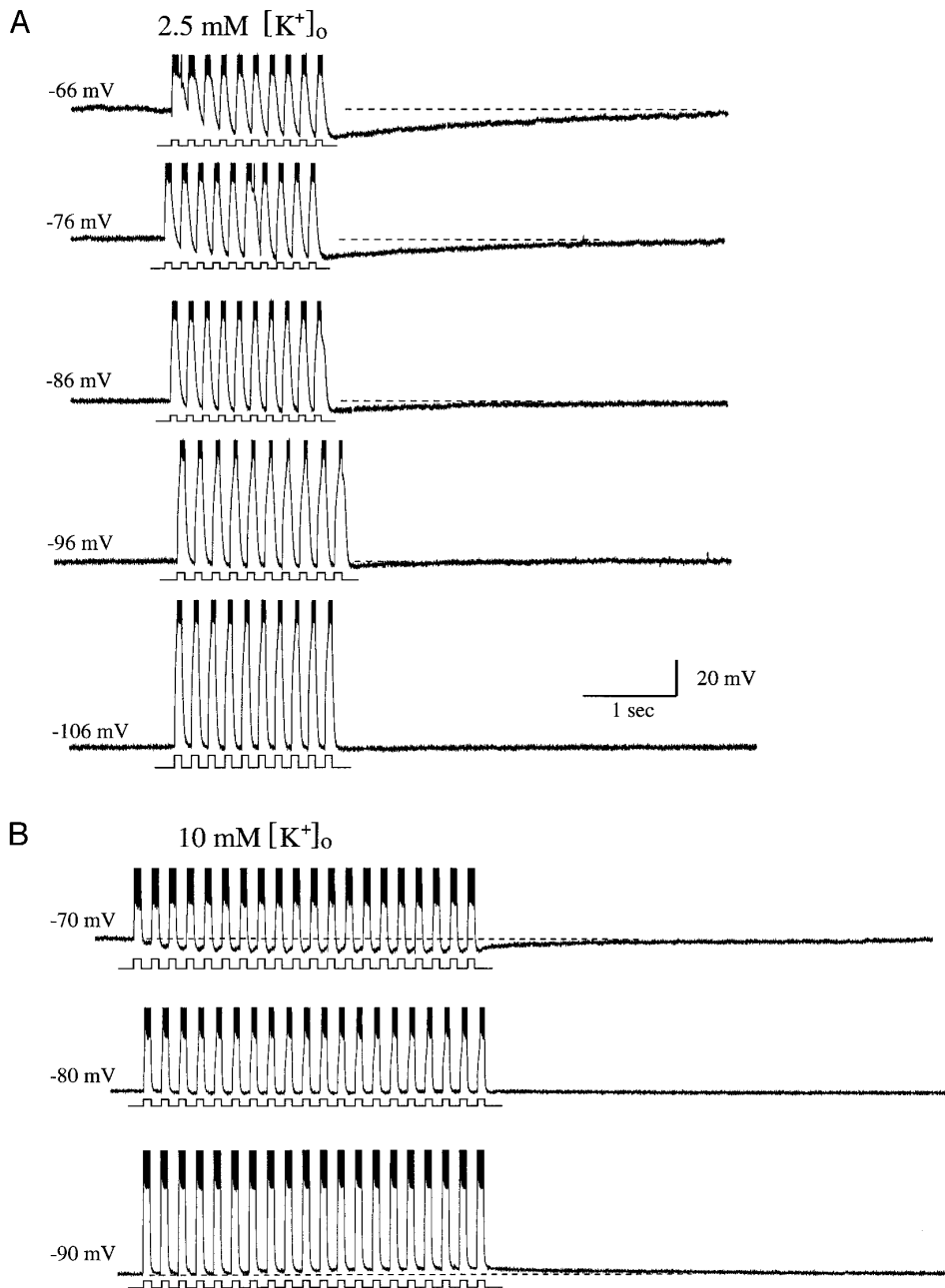


FIG. 3. Reversal potential of the post-burst AHP is sensitive to the extracellular concentration of K^+ . *A*: in the presence of 2.5 mM external potassium ions, the AHP after repetitive bursts of action potential generation exhibits a projected reversal potential of -106 mV. *B*: after elevation of external potassium concentration to 10 mM, the AHP reverses in polarity at around -80 mV, indicating that activation of potassium currents mediates the AHP generation.

RESULTS

Intracellular recordings were obtained from 147 PGN cells in ferret geniculate slices maintained *in vitro*. A representative sample of 10 of these neurons exhibited an average resting membrane potential of -61 ± 6 (SD) mV and apparent input resistance of 137 ± 25 M Ω , as measured by the electrotonic response to a 0.1- to 0.2-nA hyperpolarizing current pulse at resting membrane potentials.

During the generation of spindle waves, PGN cells received cyclic barrages of excitatory postsynaptic potentials (EPSPs). Many of these EPSP barrages were successful in the activation of a low-threshold Ca^{2+} spike and associated burst discharges (Fig. 1A), as reported previously (Bal et al. 1995a,b; Mulle et al. 1986). With the generation of spindle waves, PGN neurons typically exhibited a progressive hyper-

polarization that persisted as an afterhyperpolarization (AHP) of 10–20 mV during the spindle wave refractory period. The duration of the slow AHP typically matched the duration of the spindle wave refractory period (Fig. 1A). The intracellular injection of brief hyperpolarizing current pulses into PGN cells during the AHP revealed that their apparent input resistance is diminished immediately after the cessation of the spindle wave and that this decrease in apparent input resistance recovers as the AHP lessens (Fig. 1B). Controlling for the change in membrane potential during the AHP revealed that the change in apparent input resistance resulted both from the activation of an outward current (Fig. 1C) as well as to voltage-dependent changes in apparent input resistance of these cells (Bal and McCormick 1993). Compensating for changes in the membrane potential with the injection of current in three cells revealed that the input

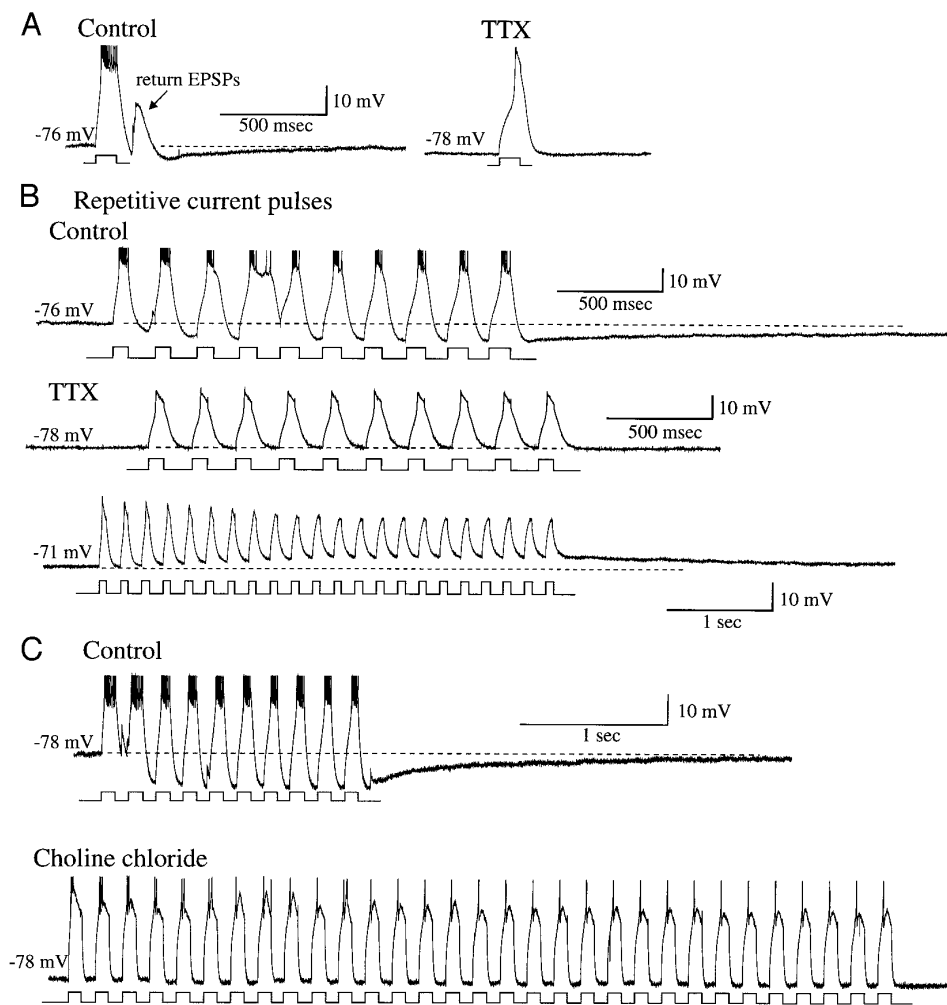


FIG. 4. Action potential generation potentially facilitates the generation of the progressive hyperpolarization and slow AHP. Action potentials are truncated. *A*: generation of a single burst of action potentials by intracellular injection of depolarizing current pulse is followed by hyperpolarization that is interposed by return EPSPs arising from dorsal lateral geniculate nucleus (LGNd) cells through disynaptic loops (see text). Application of TTX ($10 \mu\text{M}$ in micropipette) near the PGN cell results in the abolition of action potentials and an abolition of the burst AHP. *B*: repetitive induction of bursts of action potentials is accompanied by a progressive hyperpolarization in membrane potential and is followed by a slow AHP that lasts 5–10 s. Block of action potentials with tetrodotoxin (TTX) application results in abolition of the progressive hyperpolarization and the slow AHP. Indeed, the repetitive induction of the low-threshold calcium spikes at a more depolarized membrane potential is accompanied with a progressive depolarization that generates an afterdepolarization. *C*: progressive hyperpolarization and slow AHP are abolished following reduction of $[\text{Na}^+]_o$ to 26 mM by replacing NaCl with choline chloride in the bathing solution.

resistances measured at 3 s after the cessation of spindle waves were decreased to 79, 82, and 86% on average of those measured at 10 s after the termination of the previous spindle wave ($P < 0.001$). Mimicking the arrival of barrages of EPSPs with the intracellular injection of a depolarizing current pulse revealed that the slow AHP may potentially regulate the responsiveness of these neurons to this input (Fig. 1*D*). Immediately after the generation of a spindle wave, the AHP was associated with a decreased depolarizing response to the constant current pulse (Fig. 1*Da*). However, as the AHP lessened, the electrophysiological response to the depolarizing current pulse became progressively larger (Fig. 1*D, b* and *c*) until, finally, a low-threshold Ca^{2+} spike was generated and the subsequent burst of action potentials in this cell initiated a spindle wave throughout the network (Fig. 1*Dd*) (Kim et al. 1995).

The progressive hyperpolarization and development of the slow AHP could be replicated in the absence of synaptic influences through the induction of repetitive burst discharges in PGN cells with the intracellular injection of current pulses, suggesting that this event may result from the activation of intrinsic membrane currents (Fig. 2). At membrane potentials negative to -60 mV, where spindle waves prevail in ferret LGNd slices in vitro, the intracellular injection of a brief depolarizing current pulse of 100

ms in duration into PGN cells triggered a low-threshold calcium spike mediated burst discharge of 10–20 action potentials in peak frequency of 450–550 Hz (Fig. 2*A*). This single burst of high-frequency action potentials was followed by an AHP of ~ 5 mV in amplitude that was sustained for ≤ 1 s. The induction of repetitive burst discharges at 6 Hz by current pulse injection (in simulation of oscillatory burst discharges during spontaneous generation of spindle waves) was accompanied by a progressive hyperpolarization of the membrane potential and the generation of a 10–15 mV, 5–10 s slow AHP (Fig. 2*B*). This AHP appeared to decay in two phases, indicating early and late components (Fig. 2*A*).

Depolarizing the membrane potential of PGN cells above -60 mV resulted in the inactivation of the low-threshold calcium current. At these membrane potentials the intracellular injection of a depolarizing current pulse failed to activate burst discharges but rather produced tonic trains of action potentials (Fig. 2*C*). The AHP that followed tonic discharge also exhibited early and late components (Fig. 2*C*). The amplitude and duration of the slow AHP after tonic discharge induced by the injection of a 1-s duration current pulse increased with increasing rate of action potential generation, reaching up to 10 s in duration and 20 mV in amplitude after a discharge at 100–150 Hz for 1 s (Fig. 2*D*).

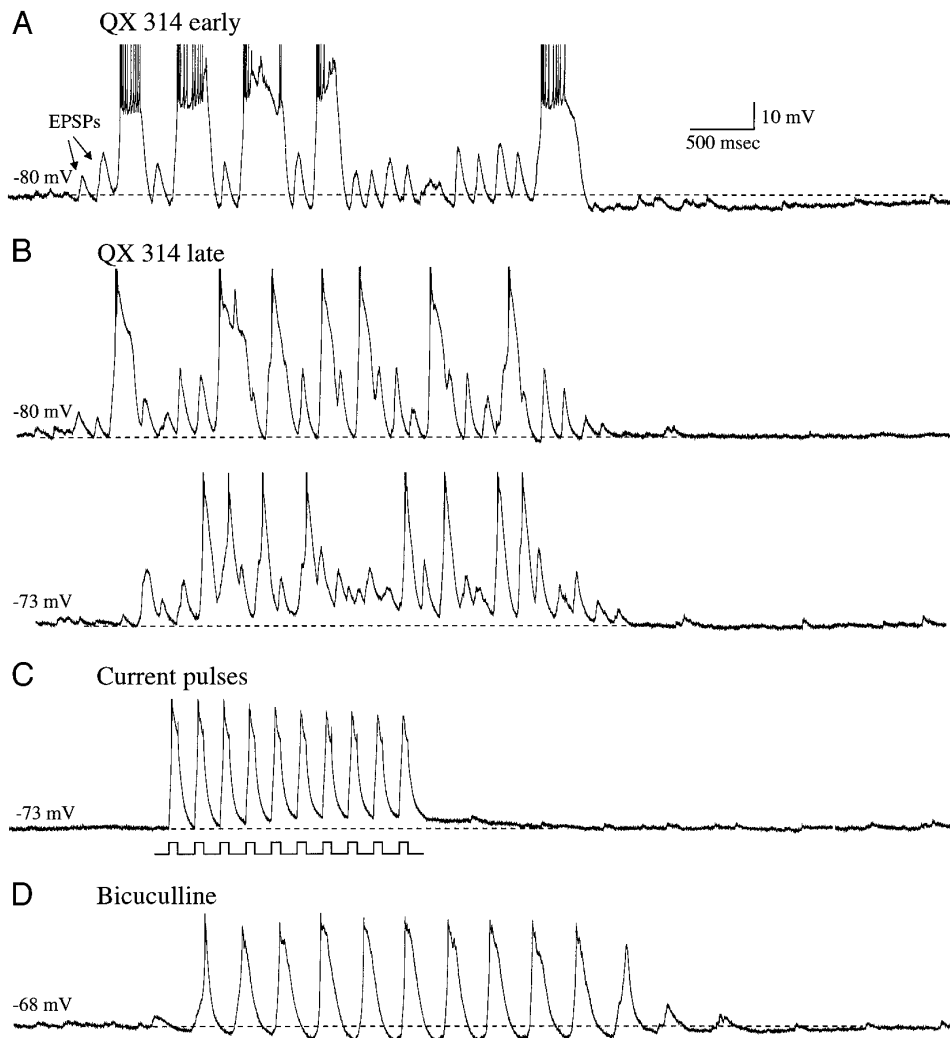


FIG. 5. Occurrence of action potentials are important for the generation of the spindle wave AHP. Action potentials are truncated. *A*: perigeniculate nucleus neurons were recorded with intracellular electrodes containing 30 mM QX-314. After 10 min of recording, a volley of EPSPs arising from LGNd cells still activates burst discharges of action potentials during the generation of spindle waves, and this is followed by an AHP. *B*: after 30 min, when intracellular QX-314 takes its full effect and blocks action potential generation, the EPSPs impinging on PGN cells activate only the low-threshold calcium spikes in rhythmic occurrence without progressive hyperpolarization or AHP activation. At a more depolarized membrane potential (-73 mV), the superimposition of EPSPs and occasional discharges of low-threshold calcium spikes develops a depolarizing envelope during the spindle wave. *C*: induction of repetitive discharges of low-threshold calcium spikes by injecting current pulses is accompanied with a progressive depolarization of the membrane potential that persists as a small afterdepolarization. *D*: bath infusion of $30 \mu\text{M}$ bicuculline methiodide converts spindle oscillation into a slowed oscillation. Even pronounced activation of low-threshold calcium spikes at every cycle does not evoke an AHP. Scale in *A* applies to *B–D*.

To identify the membrane current that underlies the slow AHP, the reversal potential of this event was determined (Fig. 3A). To activate the slow AHP, PGN cells were induced to discharge repetitive bursts of action potentials with an interburst frequency of 7 Hz with the intracellular injection of repetitive depolarizing pulses. The voltage dependence of the slow AHP then was examined by hyperpolarizing the membrane potential to different levels while maintaining approximately the same number and intensity of burst discharges (Fig. 3A). In this manner, the AHP amplitude decreased as the membrane potential was hyperpolarized, finally disappearing at a membrane potential of around -105 mV. Increasing $[\text{K}^+]_o$ from 2.5 to 10 mM resulted in a shift of ~ 25 – 30 mV in the apparent reversal potential from -105 mV to -80 mV ($n = 3$; Fig. 3B). A similar magnitude of shift (35 mV) is expected from the Nernst equation if the AHP were mediated by a pure potassium current.

Slow AHP is not Ca^{2+} dependent

Previous investigations of the electrophysiological properties of thalamic reticular cells have shown that low-threshold Ca^{2+} spikes can result in the generation of a Ca^{2+} -activated K^+ current and therefore a postburst AHP (Avanzini et al.

1989; Bal and McCormick 1993). Here we examined the possibility that the slow AHP in PGN neurons after repetitive burst firing resulted from increases in $[\text{Ca}^{2+}]_i$ from the generation of low-threshold Ca^{2+} spikes.

In normal solution, the induction of a single burst of action potentials by the injection of a depolarizing current pulse into a PGN cell generated an AHP of ~ 1 s in duration (Fig. 4A). Superimposed on this AHP are ‘‘return EPSPs’’ that are generated by the PGN-induced rebound burst firing of connected thalamocortical cells (Bal et al. 1995b; Kim et al. 1995). The return EPSPs were observed in 20–30% of recorded PGN cells. The local application of TTX ($10 \mu\text{M}$ in micropipette) in proximity to the PGN cell resulted in a block of action potential generation, thereby isolating the low-threshold Ca^{2+} spikes (Fig. 4A, TTX). The activation of repetitive low-threshold Ca^{2+} spikes after the application of TTX failed to generate a slow AHP and in fact typically resulted in the generation of a slow afterdepolarization (Fig. 4B).

Similar to the results obtained by blocking action potential generation with TTX, reducing $[\text{Na}^+]_o$ from 156 to 26 mM by substituting choline chloride for NaCl also resulted in an abolition of the slow AHP (Fig. 4C), even though low-threshold Ca^{2+} spikes were still generated. In addition, blocking the generation of action potentials by including 30

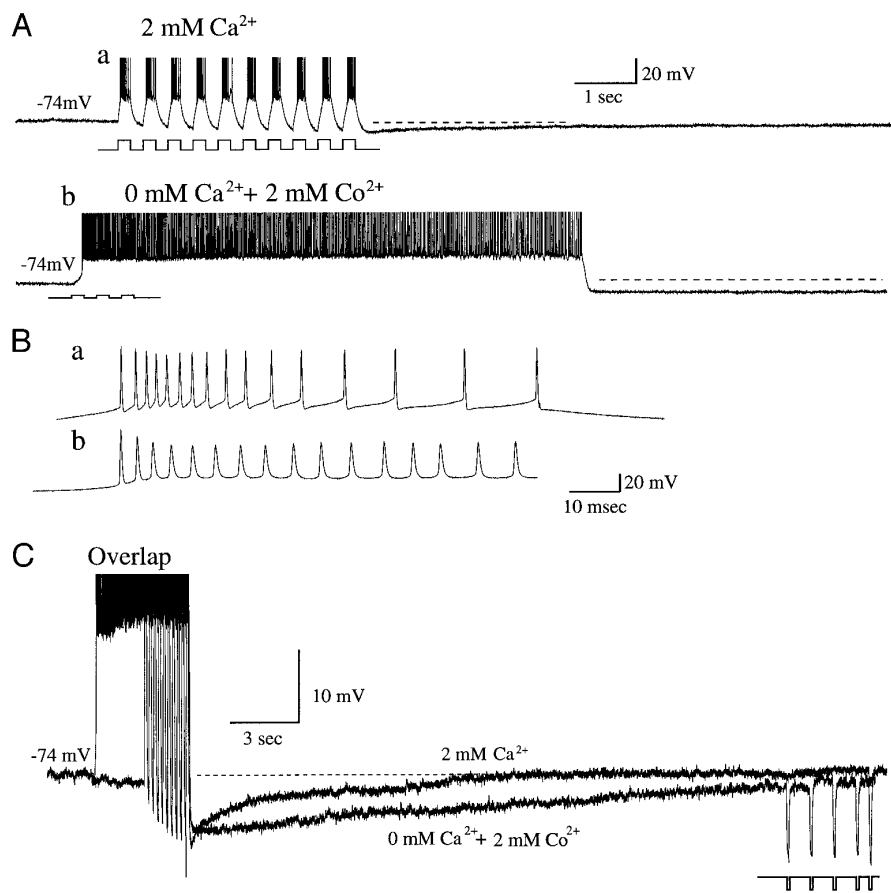


FIG. 6. Block of Ca^{2+} currents reduces the early, but not the late, components of the AHP. *A*: repetitive generation of burst discharges is followed by a slow AHP. When the influx of Ca^{2+} is blocked by replacing Ca^{2+} with Co^{2+} the burst pattern of action potential is converted into a prolonged discharge of action potentials that is followed by a slow AHP. *B*: expansion of the initial barrage of action potentials before and after block of Ca^{2+} spikes illustrating the reduction of single spike AHPs. *C*: overlap of AHPs activated in control and in calcium-free solution. After block of Ca^{2+} currents, the AHP decays more slowly, although it now is generated by the discharge of more action potentials.

mM QX-314 in the intracellular recording electrodes also resulted in a block of the slow AHP that follows spindle wave generation (Fig. 5, *A* and *B*). After the block of Na^+ action potentials, the intracellular injection of repetitive depolarizing current pulses resulted in the generation of low-threshold Ca^{2+} spikes but not a slow AHP (Fig. 5*C*). Even the bath application of bicuculline ($30 \mu\text{M}$), which converts spindle waves into a slow oscillation in which PGN cells typically exhibit large AHPs (Bal et al. 1995a,b), did not result in an AHP if Na^+ action potentials were blocked with QX-314 (Fig. 5*D*). Taken together, these results demonstrate that discharge of low-threshold calcium spikes alone is not sufficient to activate the slow AHP in PGN cells.

Two possible explanations of these results are that the slow AHP is activated by the entry of Na^+ during action potential generation (Schwindt et al. 1989) or from the entry of Ca^{2+} through high-threshold Ca^{2+} channels (Constanti and Sim 1987; Lancaster and Adams 1986; Sah 1996; Storm 1993). To test the possibility that the slow AHP results from the entry of Ca^{2+} during action potential generation, we blocked Ca^{2+} entry by removing Ca^{2+} from the bathing solution and adding 2 mM Co^{2+} , a potent blocker of high-threshold Ca^{2+} channels (Hagiwara and Takahashi 1967; Ryu and Randic 1990; Winegar et al. 1991).

In "calcium-free" solution containing 2 mM cobalt ions, intracellular injection of brief depolarizing current pulses resulted in a 10- to 20-s duration plateau potential and the generation of action potentials (Fig. 6*A*; $n = 5$). Individual action potentials after wash in of calcium-free solution con-

taining 2 mM Co^{2+} were broadened significantly in duration and did not exhibit the typical fast AHP (Fig. 6*B*), presumably owing to the block of fast Ca^{2+} -activated K^+ currents (Jahnsen and Llinas 1984a,b). Despite the apparent block of Ca^{2+} currents, the residual discharge in PGN neurons was associated with a pronounced slow AHP (Fig. 6*A*). The main difference between the AHPs before and after wash in of calcium-free solution containing 2 mM Co^{2+} was the reduction of an early component of the slow AHP and a prolongation of the slow component, presumably owing to the increase in discharge of the PGN neuron (Fig. 6*C*).

The possibility that the slow AHP was generated in response to Na^+ and not Ca^{2+} entry was further examined by promoting the occurrence of high-threshold Ca^{2+} spikes through the bath application of 10 mM tetraethylammonium (TEA) (Fig. 7). Bath application of TEA resulted in the generation of prolonged plateau potentials and a slow AHP in PGN neurons in response to the intracellular injection of a depolarizing current pulse (Fig. 7, *B* and *C*). Block of Na^+ -dependent action potentials with the local application of TTX resulted in a marked reduction in the slow AHP, even though the intracellular injection of repetitive depolarizing current pulses generated a significantly greater number of Ca^{2+} spikes ($n = 5$ cells; Fig. 7*D*). For example, comparing the slow AHP after repetitive burst firing in Fig. 7*A* with the slow AHP remaining after the application of TEA and TTX revealed that the generation of even 44 Ca^{2+} spikes is insufficient to generate an AHP as large as that after 10 bursts of action potentials in normal solution (Fig. 7*E*).

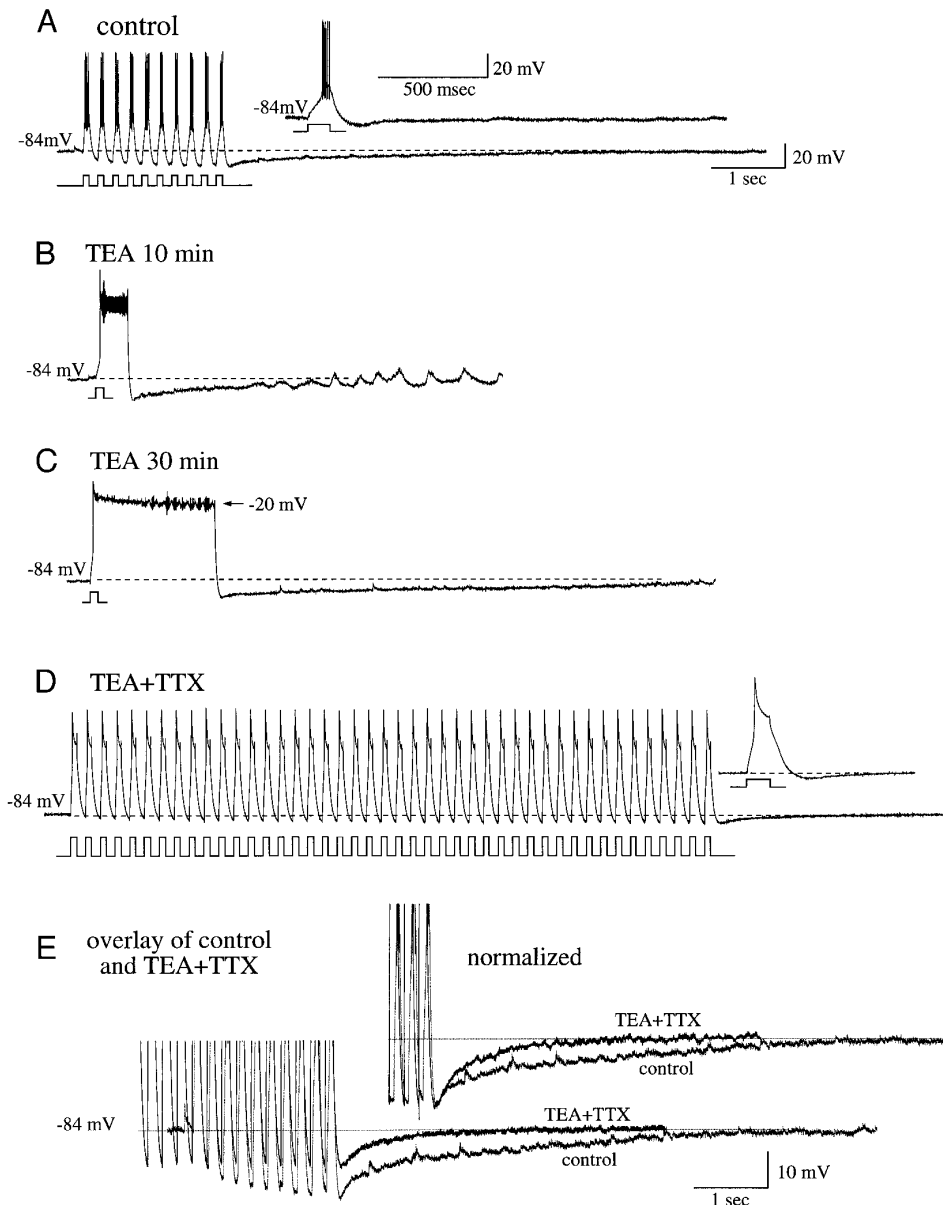


FIG. 7. Slow AHP depends on the activation of action potentials and is not generated by repetitive Ca^{2+} spikes. *A*: repetitive activation of low-threshold Ca^{2+} spike mediated bursts of action potentials is followed by the slow AHP. *B* and *C*: addition of 10 mM tetraethylammonium to the bathing medium results in the generation of a prolonged plateau potential and tonic discharge. Cessation of this activity is also followed by a slow AHP. *D*: local application of TTX (10 μM in micropipette) results in the generation of a Ca^{2+} spike alone with each depolarizing current pulse. Despite the generation of 40 Ca^{2+} spikes, there is only a small and short lasting AHP. *E*: overlap of the AHPs after repetitive generation of bursts of action potentials (*A*) and calcium spikes (*D*). *Inset*: peak amplitude of AHP after discharges of calcium spikes (*D*) is normalized to the peak amplitude of AHP activated by repetitive bursts of action potentials (*A*). Note that the AHP activated by calcium spikes is smaller and much shorter in duration in comparison with the slow AHP generated by only 10 action potential bursts. Scale in *A* applies to *B–D*.

With a block of action potential generation, the duration of the AHP decreased to 20–40% of control, whereas the peak amplitude was reduced to 30–70% of control ($P < 0.001$; $n = 5$). In one cell, the slow AHP could not be activated after the application of TTX even though the current pulse injection activated prominent calcium spikes.

Contribution of a persistent Na^+ current to plateau potentials

The sustained discharge of action potentials in calcium-free solution in response to a transient current pulse and development of prolonged depolarizing plateau potential in 10 mM TEA imply the presence of a persistent sodium current in PGN cells, the expression of which is restrained by potassium currents. To visualize antagonistic influences between the persistent sodium and potassium currents on burst profile of action potential generation, PGN cells were

impaled with electrodes filled with 2 M cesium acetate so as to reduce potassium currents from inside the cell.

At an early stage of recording, the intracellular injection of a depolarizing current pulse resulted in a discharge of the transient low-threshold calcium spike mediated burst of action potentials (Fig. 8*A*). As cesium ions diffused into the cell and began to suppress potassium currents, the current injection gave rise to progressively prolonged plateau potentials and tonic discharge. After prolonged depolarization, fast action potentials may inactivate, revealing the plateau potential alone (Fig. 8*A*, 35 min). Local application of TTX resulted in a gradual block of the plateau potential, finally revealing only the generation of a low-threshold Ca^{2+} spike ($n = 4$; Fig. 8*B*).

In a subset of PGN cells (13 of 42 cells tested), the injection of either depolarizing or hyperpolarizing current pulses activated a prolonged burst of action potentials, even in normal bathing solution and with recording electrodes

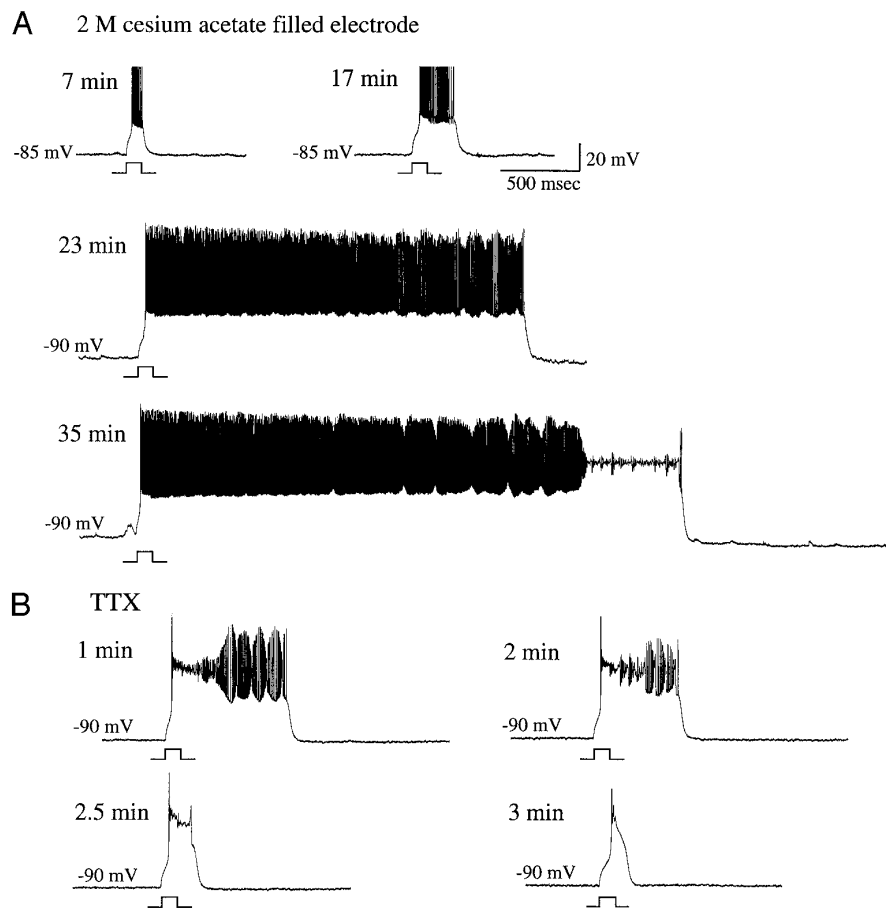


FIG. 8. Plateau potentials are generated through the activation of a persistent Na^+ current. *A*: perigeniculate neuron was impaled with an electrode filled with 2 M cesium acetate. During the course of recording, as intracellular cesium ions block potassium currents, a brief depolarizing current injection produces gradually elongated bursts of action potentials and a plateau potential. *B*: local application of TTX blocks the generation of action potentials and the plateau potential. Scale in *A* applies to *B*.

that contained 2 M KAc (Fig. 9A). These discharges consisted of a high-frequency burst followed by a prolonged and tonic train of action potentials. Local application of TTX ($10 \mu\text{M}$ in the micropipette) blocked not only the generation of fast action potentials but also the prolonged depolarization after the generation of the burst, revealing only a residual low-threshold Ca^{2+} spike (Fig. 9A; $n = 3$). Interestingly, the application of TTX also resulted in a reduction in the rate of rise of the low-threshold Ca^{2+} spike (Fig. 9A), indicating that the persistent Na^+ current modulates the rate of rise, as well as the duration, of these events (Fig. 9B).

Those perigeniculate cells that exhibited a burst followed by the prolonged generation of tonic action potentials in response to current pulses also often generated prolonged trains of action potentials during the occurrence of spindle waves even with normal recording microelectrodes (Fig. 9C). These burst-tonic patterns of activity could result in a progressive depolarization of PGN cells (6 of 13 cells) during the generation of the spindle wave, although the cessation of the spindle wave was followed by a pronounced AHP (Fig. 9C).

The prolongation of a burst discharge of action potentials through activation of persistent sodium current in a subset of PGN cells in normal condition and in other PGN cells after suppression of potassium currents indicated that the shape of burst generation of action potentials is molded by concerted activation of multiple currents, including the low-threshold calcium current, persistent sodium current, and multiple potassium currents. To investigate how different

potassium currents influence a burst profile of action potential generation, we applied specific channel blockers to PGN cells and examined their effects.

Application of apamin ($1 \mu\text{M}$ in micropipette), a blocker of certain Ca^{2+} -activated K^+ currents (Castle et al. 1989; Dreyer 1990; Moczydlowski et al. 1988), resulted in the generation of a prolonged plateau potential after a low-threshold Ca^{2+} spike in PGN neurons as well as increasing the rate of action potential discharge during the burst itself (Fig. 10A). These effects also were seen during the generation of spindle waves, and the generation of prolonged plateau potentials during spindle waves resulted in these network oscillations being followed by larger and more prolonged slow AHPs (Fig. 10D). Local application of TTX ($10 \mu\text{M}$ in micropipette) to the PGN blocked the apamin-induced plateau potential and revealed only an underlying low-threshold Ca^{2+} spike (Fig. 10A). If apamin was applied only after TTX had been applied, then a prolongation of the low-threshold Ca^{2+} spike was observed (Fig. 10C). Although the application of apamin reduced or abolished the AHP that follows a single low-threshold Ca^{2+} spike (Fig. 10C), it either had no effect, or actually enhanced, the post-spindle wave AHP (Fig. 10D; $n = 6$).

Interestingly, the local application of the high-threshold calcium channel blocker ω -conotoxin ($1 \mu\text{M}$ in micropipette) also resulted in the generation of prolonged afterdischarges in PGN cells, both those induced by a single current pulse (Fig. 11B) as well as those associated with the genera-

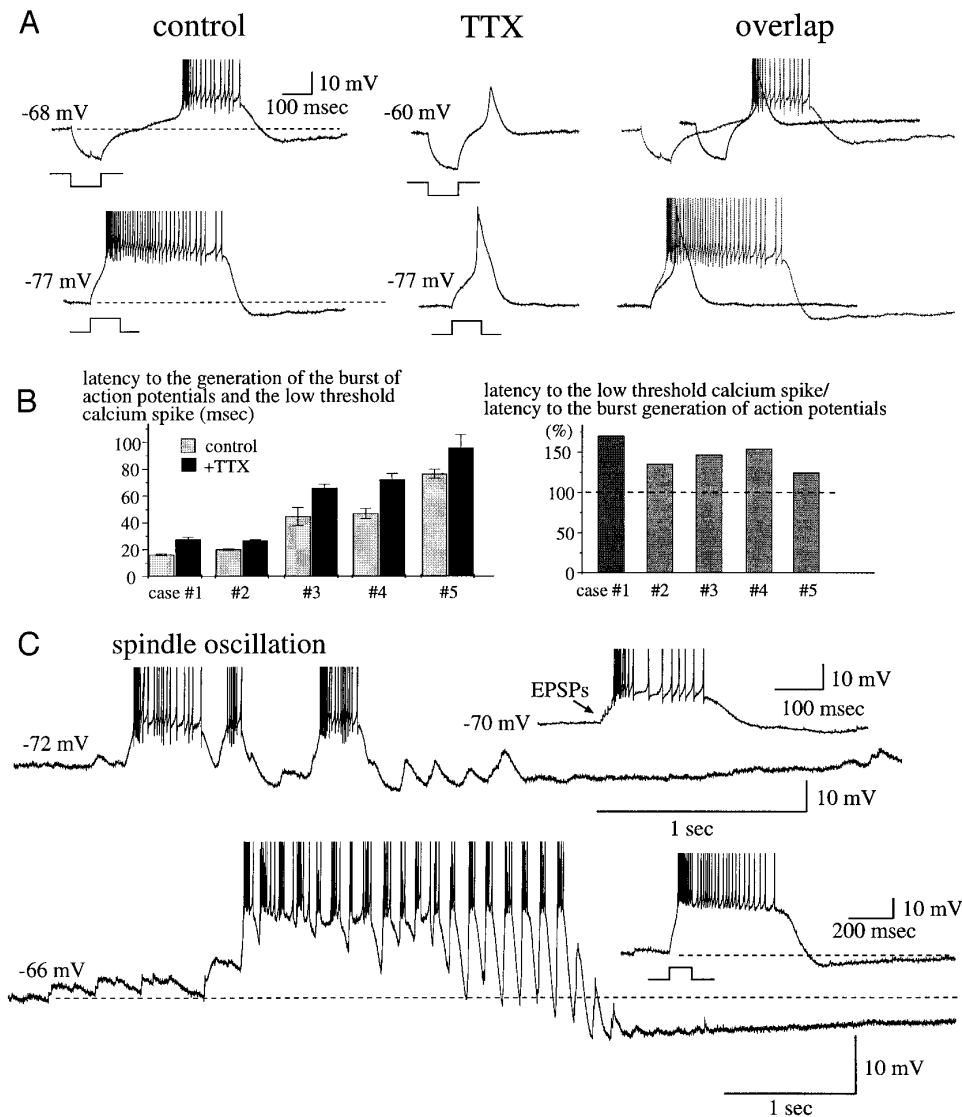


FIG. 9. Normal perigeniculate nucleus (PGN) cells can generate plateau potentials. Action potentials are truncated. *A*: intracellular injection of hyperpolarizing or depolarizing current pulses in this PGN cell generated a low-threshold Ca^{2+} spike mediated burst of action potentials followed by a plateau potential. Local application of TTX blocked the action potentials as well as the plateau potential. Overlap of the burst of action potentials and underlying low-threshold calcium spike revealed a delay in the rising slope after TTX application. *Ba*: latency to the discharge of burst and underlying low-threshold calcium spike was compared from the onset of the positive current step. Normalization of the latency revealed that the TTX application increased the latency to the generation of the low-threshold calcium spike by 130–170%. *C*: normal spindle waves in 2 different PGN cells illustrating the occurrence of bursts of action potentials followed by plateau potentials.

tion of spindle waves (Fig. 11, *F* and *G*). Again, these plateau potentials were blocked by the local application of tetrodotoxin (Fig. 11, *D* and *E*), and the application of ω -conotoxin did not abolish the slow AHP (Fig. 11, *F* and *G*; $n = 5$).

DISCUSSION

We demonstrate here that the participation of the GABAergic neurons of the ferret perigeniculate nucleus in rhythmic thalamocortical activities are influenced by at least three distinct ionic conductances, including both Ca^{2+} and Na^{+} -activated K^{+} currents and a persistent inward Na^{+} current. Each action potential in PGN neurons is followed by an AHP that is dramatically reduced by removing Ca^{2+} from the bathing medium. In addition, each low-threshold Ca^{2+} spike also is followed by an AHP that is abolished by apamin (Avanzini et al. 1989; Bal and McCormick 1993) (see Figs. 6 and 10). These results suggest that these afterhyperpolarizations are mediated at least in part by Ca^{2+} -activated K^{+} currents, as in other cell types (Bal and McCormick 1997;

Rudy 1988; Storm 1993; Sah 1996; Wilcox et al. 1988). The activation of a Ca^{2+} -activated K^{+} current appears to be critically involved not only in the generation of an AHP but also in determining the duration of low-threshold Ca^{2+} spikes in these GABAergic neurons (e.g., Fig. 10). The duration of burst firing in PGN neurons has the important consequence of determining the functional state of the thalamic network (Bal et al. 1995a,b; Kim et al. 1997). Recently, we have demonstrated that prolonged burst firing in PGN neurons may result in the strong activation of γ -aminobutyric acid-B (GABA_B) receptors (Kim et al. 1997) and that this strong activation of GABA_B receptors converts spindle waves into 3-Hz slow oscillations that resemble abnormal "paroxysmal" rhythms reported in various animal models and in human patients with generalized absence seizures (Sanchez-Vives and McCormick 1997; Sanchez-Vives et al. 1997). Therefore the regulation of Ca^{2+} -activated K^{+} currents may be critical to the determination of functional states in thalamocortical networks.

In addition to the AHPs following single action potentials or single low-threshold Ca^{2+} spikes, there also appeared a

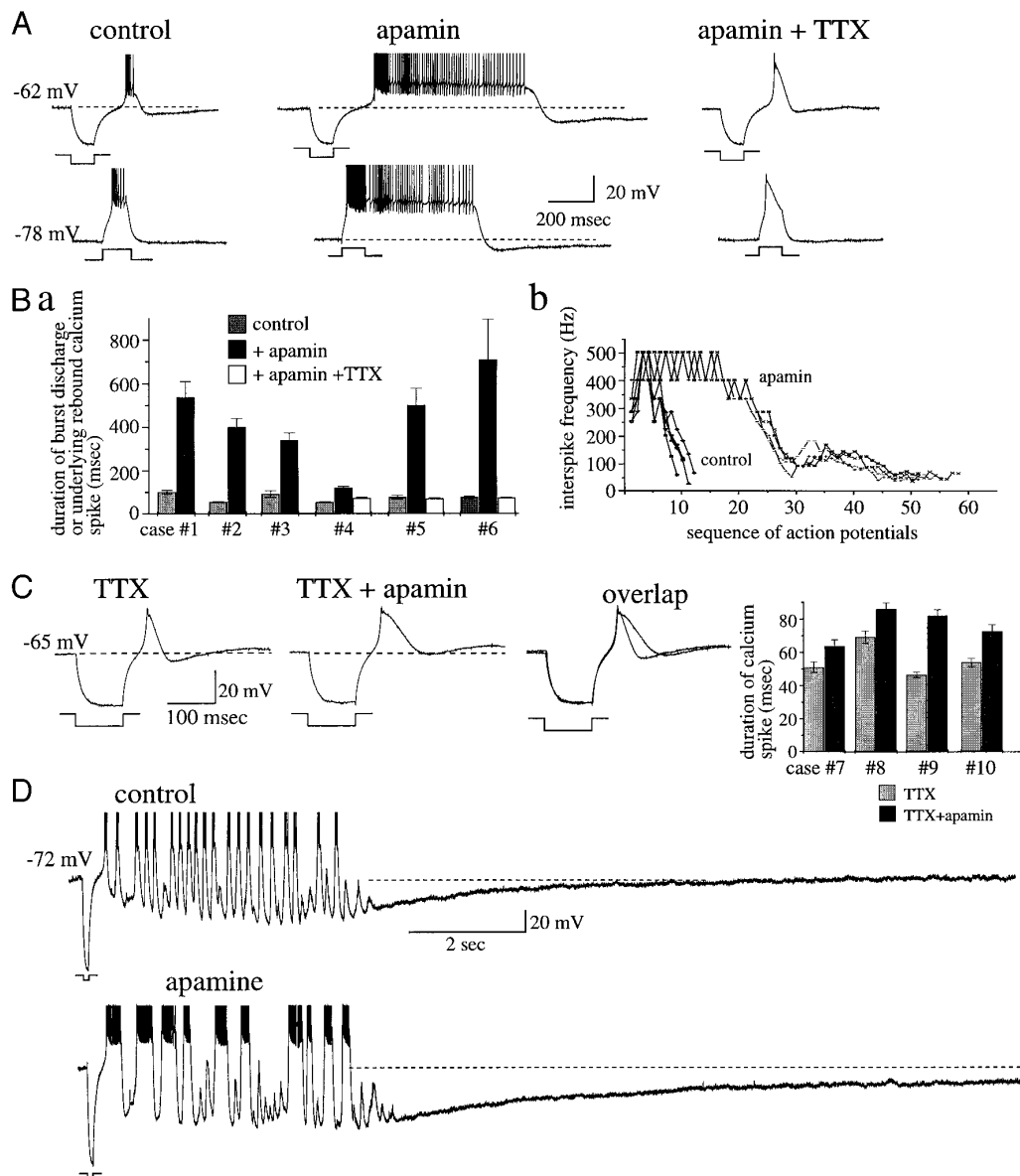


FIG. 10. Block of Ca^{2+} -activated K^+ currents with apamin promotes the occurrence of plateau potentials. Action potentials are truncated. *A*: intracellular injection of hyperpolarizing or depolarizing current pulses results in the generation of low-threshold Ca^{2+} spike mediated bursts of action potentials. Local application of apamin ($1 \mu\text{M}$ in micropipette) results in the block of the burst AHP and the appearance of prolonged plateau potentials, which are blocked by local application of TTX. These results are summarized as histograms (*Ba*). Burst and plateau potential were induced through the injection of a hyperpolarizing current pulse. *Bb*: apamin application led to a prolongation of the burst core of high-frequency action potentials and the generation of low-frequency tonic action potentials associated with the plateau potential. *C*: application of apamin in the presence of TTX reduces the Ca^{2+} spike AHP and prolongs the Ca^{2+} spike. As illustrated in the histogram, the duration of the rebound calcium spike increased by 130–170% of control. *D*: application of apamin ($1 \mu\text{M}$ in micropipette) to the region of this PGN neuron results in the generation of plateau potentials during the generation of spindle waves, which were evoked by rebound burst firing by this cell.

long-lasting (5–15 s) hyperpolarization of the membrane potential after the generation of repetitive burst or tonic action potential activity. This AHP appears to be mediated by the activation of one or more K^+ currents because it is associated with an increase in membrane conductance and its reversal potential is sensitive to $[\text{K}^+]_o$. We suggest that there are at least two distinct components to this AHP. The initial portion of the AHP may be mediated through the activation of a Ca^{2+} -activated K^+ current because it is reduced after block of calcium influx into PGN cells (Fig.

6C) and persists after the block of voltage-dependent Na^+ currents with application of tetrodotoxin (Fig. 7E). This initial portion of the AHP lasts on the order of 1–3 s and presumably is similar to the AHPs found in other central neurons and which result from Ca^{2+} -activated K^+ currents (Constanti and Sim 1987; Lancaster and Nicoll 1987; Schwandt et al. 1988; Storm 1989). However, a slow AHP persists in PGN neurons after the block of Ca^{2+} currents, and our data indicate that this AHP is generated through the activation of a Na^+ -activated K^+ current.

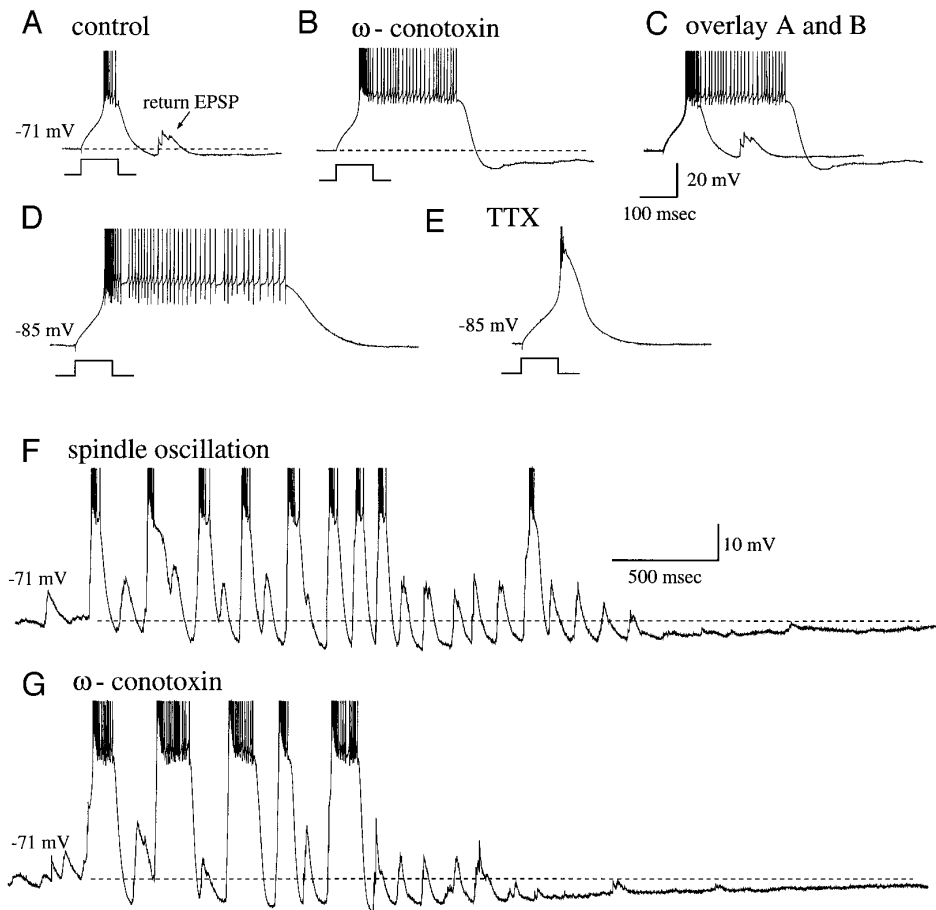


FIG. 11. Application of the Ca^{2+} channel blocker ω -conotoxin has effects similar to apamin. Action potentials are truncated. *A*: local application of the N-type channel antagonist ω -conotoxin ($1 \mu\text{M}$ in micropipette) results in the generation of plateau potentials (*B*). *C*: overlay of *A* and *B* for illustration. *D*: block of voltage-dependent Na^+ channels with the local application of TTX blocks the plateau potential and reveals the low-threshold Ca^{2+} spike. *F*: normal spindle wave recorded in this PGN cell before application of ω -conotoxin. *G*: application of ω -conotoxin ($1 \mu\text{M}$ in micropipette) results in the generation of plateau potentials during spindle wave generation.

Prior studies have demonstrated Na^+ -activated K^+ currents in a variety of excitable cells including cardiac myocytes, chick sensory ganglion neurons, and cortical pyramidal cells (Dryer 1994; Egan et al. 1992a,b; Foehring et al. 1989; Kameyama et al. 1984; Safronov and Werner 1996; Schwindt et al. 1989). Using slices of cat sensorimotor cortex in vitro, Schwindt, Crill and colleagues demonstrated a prominent AHP after prolonged stimulation of action potentials in layer V Betz pyramidal cells (Foehring et al. 1989; Schwindt et al. 1989). The ionic mechanisms for the generation of this AHP appear to be similar in many aspects to the one that we have observed in PGN cells with the early and late components of AHP being mediated largely by calcium- and sodium-dependent potassium currents, respectively.

Direct examination of Na^+ -activated K^+ channels in various cell types has demonstrated that these channels require an increase in intracellular Na^+ of ≥ 10 – 20 mM for their activation (see Dryer 1994). It is doubtful that this high level of $[\text{Na}^+]_i$ is ever reached during normal activity, and therefore the role of these channels is controversial. One possibility is that the methods used to examine the properties of these channels, namely excised patches or whole cell recording techniques, may have disrupted their normal properties resulting in a significant reduction in sensitivity to $[\text{Na}^+]_i$. Alternatively, the Na^+ -activated K^+ channels that underlie the ionic current of the slow AHP examined here may represent a class of ionic channel that is distinct from those previously examined at the single channel level. These possibilities remain to be explored.

Our results suggest a complex role for the slow AHP in determining the pattern of activity in PGN cells. During the generation of spindle waves, the progressive hyperpolarization of the membrane potential results in an initial enhancement of burst firing through removal of inactivation of the low-threshold Ca^{2+} spike. However, as the hyperpolarization deepens, EPSP barrages may become subthreshold for activation of low-threshold Ca^{2+} spikes. We previously have proposed that this hyperpolarization of PGN neurons may contribute to the waxing and waning of spindle wave generation (von Krosigk et al. 1993). In addition, the prolonged time course of the slow AHP may allow it to contribute to the refractory period between episodes of spindle waves by depressing excitability of PGN cells. Indeed, our periodic injection of current pulses into PGN cells revealed a reduction in the excitability of PGN cells that gradually recovered over time during the interspindle refractory period. Recently we have demonstrated that a slow depolarization of thalamocortical neurons, resulting from the persistent activation of the hyperpolarization-activated cation current I_h , contributes to the spindle wave refractory period (Bal and McCormick 1996). Taken together, the present results indicate that the hyperpolarization of PGN cells as well as the depolarization of LGNd thalamocortical cells both contribute to the spindle wave refractory period. However, the finding that the block of I_h with extracellular application of Cs^+ (Bal and McCormick 1996) or ZD7288 (Luthi et al. 1998)

results in a complete block of the spindle wave refractory period indicates that the hyperpolarization of PGN cells by itself is insufficient to result in the cessation of spindle wave generation.

The possible role of hyperpolarization of GABAergic neurons in the PGN or thalamic reticular nucleus in the generation of spindle wave refractory period in vivo remains to be determined. Available intracellular recordings in vivo from cat nRt neurons, under barbiturate anesthesia, demonstrate that these cells actually progressively depolarize during the generation of spindle waves (Contreras and Steriade 1996; Mulle et al. 1986). This progressive depolarization during spindle waves was abolished completely after intracellular injection of QX-314 and was replaced with a hyperpolarizing envelope associated with discharges of the low-threshold calcium spikes. These results indicate that slowly growing and decaying depolarization associated with spindle sequences in vivo may be mediated through activation of the persistent sodium current, as we have observed in a minority of PGN neurons in vitro. In addition, extracellular recordings of nRt neurons in vivo in the naturally sleeping cat often reveal a period of tonic activity following the generation of a spindle wave, indicating a prolonged period of depolarization in these neurons (Steriade et al. 1986). Our results suggest that this prolonged depolarization may be due to either a persistent Na^+ current or a Ca^{2+} -activated nonselective cation current (Bal and McCormick 1993). In any case, the cessation of the persistent inward current may be followed by a prolonged hyperpolarization in vivo through the mechanisms revealed here. Other possible origins of the prominent presence of a large hyperpolarization with intracellular recordings in vitro and the lack of such with intracellular recordings in vivo are the absence of corticogeniculate inputs in vitro, differences in the properties of PGN versus nRt neurons, the presence of neuromodulatory substances in vivo that are not released in vitro, and differences in the input resistance of nRt and PGN neurons in vivo and in vitro (Contreras et al. 1993, 1996). At present it is unclear which, if any, of these may explain the differences observed between in vivo and in vitro recordings. However, it is clear from the present studies that PGN neurons possess a powerful afterhyperpolarizing mechanism that may strongly modulate the membrane potential and excitability of these cells, and in so doing, may contribute to the generation of the low frequency components of rhythmic activity in thalamocortical systems.

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