Fast Rhythmic Bursting Can Be Induced in Layer 2/3 Cortical Neurons by Enhancing Persistent Na\textsuperscript{+} Conductance or by Blocking BK Channels

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Submitted 18 July 2002; accepted in final form 29 October 2002

Traub, Roger D., Eberhard H. Buhl, Tengis Gloveli, and Miles A. Whittington. Fast rhythmic bursting can be induced in layer 2/3 cortical neurons by enhancing persistent Na\textsuperscript{+} conductance or by blocking BK channels. J Neurophysiol 89: 909–921, 2003; 10.1152/jn.00573.2002. Fast rhythmic bursting (or “chattering”) is a firing pattern exhibited by selected neocortical neurons in cats in vivo and in slices of adult ferret and cat brain. Fast rhythmic bursting (FRB) has been recorded in certain superficial and deep principal neurons and in aspiny presumed local circuit neurons; it can be evoked by depolarizing currents or by sensory stimulation and has been proposed to depend on a persistent $g_{\text{Na}}$, that causes spike depolarizing afterpotentials. We constructed a multicompartment 11-conductance model of a layer 2/3 pyramidal neuron, containing apical dendritic calcium-mediated electrogensis; the model can switch between rhythmic spiking (RS) and FRB modes of firing, with various parameter changes. FRB in this model is favored by enhancing persistent $g_{\text{Na}}$ and also by measures that reduce $[\text{Ca}^{2+}]$, or that reduce the conductance of $g_{\text{KCa}}$ (a fast voltage- and Ca\textsuperscript{2+}-dependent conductance). Axonal excitability plays a critical role in generating fast bursts in the model. In vitro experiments in rat layer 2/3 neurons confirmed (as shown previously by others) that RS firing could be switched to fast rhythmic bursting, either by buffering $[\text{Ca}^{2+}]$, or by enhancing persistent $g_{\text{Na}}$. In addition, our experiments confirmed the model prediction that reducing $g_{\text{KCa}}$ (with iberiotoxin) would favor FRB. During the bursts, fast prepotentials (spikelets) could occur that did not originate in apical dendrites and that appear to derive from the axon. We suggest that modulator-induced regulation of $[\text{Ca}^{2+}]$ dynamics or of BK channel conductance, for example via protein kinase A, could play a role in determining the firing pattern of neocortical neurons; specifically, such modulation could play a role in regulating whether neurons respond to strong stimulation with fast rhythmic bursts.

INTRODUCTION

During visually evoked gamma (30–70 Hz) oscillations in cats, recorded extracellularly, single neurons were observed to burst at gamma frequency, with high-intraburst firing frequency (Gray 1994). Such a firing pattern, variously called “fast rhythmic bursting” (FRB) or “chattering,” was demonstrated in intracellularly recorded cells in superficial cortical layers of in vivo cat cortex, some of which were shown to be spiny (hence presumptively excitatory) neurons (Gray and McCormick1996). These latter chattering cells responded to both visual stimulation and sufficiently large depolarizing pulses, with fast rhythmic bursts. In cat cortex in vivo, deep thalamic-projecting neurons, and also aspiny (presumed inhibitory) neurons, could also exhibit fast rhythmic bursting during depolarizing current pulses of appropriate amplitude (Steriade et al. 1998); intralaminar thalamocortical neurons in vivo can also discharge in this pattern (Steriade et al. 1993). FRB occurs intermittently in so-called stuttering cells, which are GABAergic (Gupta et al. 2000). Steriade et al. 1998) further noted high-frequency runs of presumed excitatory postsynaptic potentials (EPSPs) in cells capable of FRB, as if some FRB neurons were presynaptic to other FRB neurons. An obvious question is then: to what extent do FRB neurons contribute to the generation of (as opposed to just participation in) gamma oscillations? An understanding of the intrinsic mechanisms of FRB could be helpful (but clearly is not sufficient) in answering this question.

Rhythmic bursting, often in the gamma range, has also been observed in neocortical slices from adult ferrets (Brumberg et al. 2000) and (at somewhat lower frequencies) from cats (Nishimura et al. 2001). Interesting observations of Brumberg et al. (2000) included the following. 1) FRB could be evoked by metabotropic glutamate receptor activation. [This is interesting because metabotropic glutamate receptors are critically involved in gamma oscillations evoked by electrical stimulation; additionally, activation of metabotropic glutamate receptors, in the CA1 hippocampal region and superficial neocortex in vitro, can evoke gamma oscillations (Gilles et al. 2002; Whittington et al. 1995, 1997). These receptors might also play a role in sensory-activated gamma in vivo]. 2) FRB can also be evoked by current pulses, as in vivo. 3) FRB seems to depend on generation of a fast spike afterdepolarization (ADP). 4) FRB persists in $0 \text{[Ca}^{2+}]$, 2 mM $[\text{Mn}^{2+}]$ media. 5) FRB is suppressed by reduction of Na\textsuperscript{+} conductances. 6) in contrast, the sea anemone toxin ATX II, which appears to enhance persistent Na\textsuperscript{+} conductance [at least in soma/dendritic membrane (Brand et al. 2000; Mantegazza et al. 1998)], favors FRB. Brumberg et al. (2000) suggested that the spike ADP could be...
enhanced by persistent Na$^+$ conductance, thereby promoting FRB; this idea had previously been incorporated into a two-compartment model of Wang (1999), in which persistent $g_{Na}$ was located in the dendritic compartment and a fast spike-generating mechanism in the somatic compartment. Interestingly, Brumberg et al. (2000) noted that when rhythmic spiking was converted to fast rhythmic bursting, by prolonged intracellular current injection, the width of action potentials increased, and the maximal rate of fall of the action potentials decreased—as if a K$^+$ current might have been reduced; these authors did not, however, explore which K$^+$ current could be involved.

The in vitro study of Nishimura et al. (2001) likewise showed that the spike ADP in layer III sensorimotor cortical neurons is not blocked by $g_{Ca}$ reduction, and that the ADP is enhanced by intracellular calcium chelation, and that the ADP is Na$^+$-dependent. Furthermore, replacing extracellular Ca$^{2+}$ with Mn$^{2+}$ could convert a rhythmic firing pattern to an FRB-like pattern. Friedman and Gutnick (1989) had previously shown that intracellular 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), in neocortical neurons, enhanced spike ADPs and could induce bursting that was sometimes rhythmic.

Here, we build on these previous results. We construct a detailed model of a layer 2/3 pyramidal neuron that, as a form of calibration, replicates recordings of dendritic fast and slow Ca$^{2+}$-dependent spikes, under conditions of steady dendritic depolarization. It was discovered (serendipitously) that the model would generate fast rhythmic bursting under either of two conditions, which could occur exclusively or in combination: 1) when persistent Na$^+$ conductance is increased (as shown previously by others, as noted above); or 2) when a fast voltage- and [Ca$^{2+}$]-dependent conductance, $g_{K(C)}$, is reduced. The model also suggests that the spike ADP can result in part from decremental antidromic conduction of an axonal spike, suggesting another means by which a Na$^+$ conductance could influence FRB, without necessarily involving a persistent Na$^+$ conductance. Experiments in rat neocortical slices show that a number of manipulations can convert rhythmic spiking to FRB (although at frequencies below 30 Hz, in our experimental conditions); such manipulations include the previously known (from other preparations) buffering of intracellular [Ca$^{2+}$], and enhancing persistent Na$^+$ conductance. In addition, FRB could be evoked by blocking BK channels (that are presumed to mediate $g_{K(C)}$), even independently of any enhancement of persistent Na$^+$ conductance. The data suggest that at least some of the spikes in each burst could originate in the axon distal to the initial segment. We further suggest that both Na$^+$-dependent axonal excitability and also reduction of $g_{K(C)}$ are important in FRB.

**Methods**

**Simulation methods**

The formal approach to simulating the layer 2/3 cortical pyramidal neuron was similar to that used to simulate a CA3 hippocampal pyramidal cell (Traub et al. 1994), but most of the details—in cell geometry and passive and active parameters—were different. In this study, voltages (V) are transmembrane potentials, in contradistinction to earlier studies (e.g., Traub and Miles 1995; Traub et al. 1994) in which (V) signified “voltage relative to resting potential.”

**Overall model structure.** Model structure was qualitatively based on a drawing in Major (1992), his Fig. 3.14, but with a limited number of compartments and much greater symmetry than in the real neuron. The model (Fig. 1) has eight equivalent basal dendrites, four equivalent apical obliques, an apical shaft, and equivalent superficial apical branches. There are 68 soma-dendritic compartments and 6 axonal compartments. The most proximal basal and oblique compartments, along with the two perisomatic apical shaft compartments, are called “proximal dendrites”; the outer 24 superficial apical compartments are called “distal dendrites.”

**Geometrical parameters.** The soma was a cylinder with a length of 15 μm and radius of 8 μm. All dendritic compartments had a length of 50 μm. The radius of basal and oblique dendrites was 0.5 μm. The radius of the apical shaft was 4 μm, tapering to 2 μm, while distal apical branches had a radius of 0.8 μm. The surface area of each dendritic compartment was taken to be $4\pi rl$ ($r =$ radius, $l =$ length), rather than $2\pi rl$, to allow for the contribution of spines to area. Total surface area of the soma/dendrites was 35,940 μm$^2$. The most proximal axonal compartment had a length of 25 μm and a radius of 0.9 μm. The other axonal compartments had a length of 50 μm, and a radius starting at 0.7 μm, tapering to 0.5 μm.

**Passive parameters.** Membrane capacitance $C_m$ was 0.9 μF/cm²; membrane resistivity $R_m$ was 50,000 Ω-cm² for soma-dendrites and 1,000 Ω-cm² for the axon, and internal resistivity $R_i$ was 250 Ω-cm for soma-dendrites and 100 Ω-cm for the axon. $R_{axon}$ measured at the soma, with all active currents blocked, was 69.4 MΩ.

**Dynamics of voltage and [Ca$^{2+}$] behavior.** The equations describing dynamics are standard and are here summarized briefly. As units, we shall use mV, ms, nF, μS, nA. First, the discrete version of the cable equation—an approximation to the original partial differential cable equation—describes the evolution of voltage in each compartment $k$.

![FIG. 1. Compartemental structure of model layer 2/3 pyramidal neuron.](http://jn.physiology.org/ Downloaded from)

There are 68 soma-dendritic compartments, with 8 basal dendrites and 4 apical oblique dendrites. The axon contains 6 compartments.
In Eq. 1, $C_k$ is the capacitance of compartment $k$ and $V_j$ the transmembrane voltage. The sum is taken over all compartments $m$ that are connected to compartment $k$. $g_{ionic,k}$ is the conductance (internal) between the respective compartments (with the assumption that the extracellular space is isopotential). $I_{ionic,k}$ is the transmembrane ionic current for compartment $k$: one must be careful about the sign of this term, as inward currents (which depolarize the membrane) are, by convention, negative. For the membrane potential to increase during an inward current, we need the minus sign before $I_{ionic,k}$. $I_{ionic,k}$ is the sum of the synaptic terms and “intrinsic membrane” terms. If, for the sake of simplicity, we now drop the compartment subscript $k$, the synaptic terms will be

$$g_{AMPA} V + g_{GABA_A}(V + 81)$$

In Eq. 2, $g_{AMPA}$ is the (time-dependent) $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor conductance, which has a reversal potential of 0 mV, and $g_{GABA_A}$ is the (time-dependent) $\gamma$-amino butyric acid-A (GABA_A) receptor conductance, with $-81$ mV reversal potential. Other types of synaptic conductance were not simulated.

The intrinsic membrane terms were the various ionic conductances, which we now list along with shorthand notation used (in subscripts) for distinguishing the conductances from each other. As usual, "g" stands for “conductance,” and we continue to drop the compartment-designating subscript $k$. After each conductance type, we list a reference that defines the kinetics, at least partially, along with comments. In some cases, we carried over the formalism used in a previous model, because kinetic data are either lacking or else appear too complex for use in our model. Further details are listed in the Appendix. The conductances are as follows.

1) Leak, $g_L$. We do not here distinguish between Na+ and K+ components.

2) Transient (inactivating) Na+, $g_{Na(F)}$ (“F” for “fast”). Kinetic data at 22–24°C are in Martina and Jonas (1997). We speed up the kinetics twofold and shifted the rate functions 3.5 mV. To reduce the number of parameters, we chose to use the same kinetics for $g_{Na(F)}$ in the axon and soma/dendrites. This, in turn, necessitated using sufficiently large axonal $g_{Na(F)}$ density, so that repetitive firing and antidromic spikes could occur; a similar requirement has been noted by other authors, especially when soma/dendritic $g_{Na(F)}$ density is limited (e.g., Mainen et al. 1995).

3) Persistent (noninactivating) Na+, $g_{Na(P)}$ (“P” for “persistent”) (Mittman et al. 1997). Activation is similar to $g_{Na(F)}$ but at a lower voltage threshold (French et al. 1990; Kay et al. 1998). Modeling (Wang 1999) and experimental data have suggested a role of this conductance in fast rhythmic bursting and also subthreshold oscillations (Brumberg et al. 2000; Linas et al. 1991; Nishimura et al. 2001), although fast oscillations occur in thalamic relay neurons without this current but depending on PQ calcium current(s) (Pedroarena and Linas 1997).

4) Delayed rectifier K+. $g_{KDR}$. Partial kinetic data at 20–24°C are in Martina et al. (1998). We took this conductance to be noninactivating.

5) Transient inactivating K+, $g_{K(A)}$. We used thalamocortical relay cell data (room temperature) of Huguenard and McCormick (1992), speeding up the time constants twofold.

6) A slowly activating and inactivating K+ conductance, $g_{K2}$. Kinetics were taken from Huguenard and McCormick (1992) with a twofold speed-up of time constants.

7) A muscarinic receptor-suppressed K+ conductance, $g_{K(M)}$. Kinetics were as in previous publications, e.g., Bibbig et al. (2001).

8) A fast voltage- and [Ca2+]i-dependent K+ conductance, $g_{K(C)}$. The formalism is the same as used in Traub et al. (1994), with the conductance at each time proportional to a voltage-dependent Hodgkin-Huxley-like term and also to a [Ca2+]i-dependent term, $\Gamma(\chi)$. Here, $\chi$ is [Ca2+]i in the respective compartment, in arbitrary units, and $\Gamma(\chi) = \min (0.004 \times \chi, 1.0)$. The kinetics of this conductance were different, however, than in previous publications.

9) A slow [Ca2+]i-dependent K+ conductance, $g_{K(AHP)}$ (“AHP” for “afterhyperpolarization”). Again, the formalism was as in Traub et al. (1994), although with different kinetics.

10) A low-threshold inactivating Ca2+ conductance, $g_{Ca(T)}$ (“T” for “transient”). Kinetics were taken from thalamocortical relay cell data (Huguenard and McCormick 1992), with threefold speed-up of the time constants, and using a Hodgkin-Huxley formalism rather than the constant field equation.

11) A high-threshold noninactivating Ca2+ conductance, $g_{Ca(H)}$ (“H” for “high”). Kinetics derive from Kay and Wong (1987) and are similar to previous studies (Traub et al. 1994), except for a shift of rate functions on the voltage axis. The density of this conductance is constrained by the necessity of evoking dendritic Ca2+ spikes with local current injection (Fig. 2).

12) “h” conductance (hyperpolarization-activated), $g_{AR}$ (“AR” for “anomalous rectifier”). Kinetics were taken from Huguenard and McCormick’s (1992) data, obtained at 35.5°C.

In each compartment and at each time, a particular species of conductance will assume a value that is proportional to “g” (the “total conductance” in that compartment) and also is proportional to a product of Hodgkin-Huxley variables: m*h, where 0 ≤ m, h ≤ 1, where $i$ is a positive integer, and where j is either 0 (for a noninactivating conductance) or else is 1 (for an inactivating conductance), $m$ is called the activation variable, and $h$ is called the inactivation variable.

We can now write down the sum of the intrinsic membrane terms that, in each compartment, contribute to $I_{ionic}$ in Eq. 1. By way of notation, “g” denotes the total conductance (of the subscript-designated conductance species) in the respective compartment. The intrinsic membrane current is then

$$C_dV/dt = \sum_k g_{ionic,k}(V_m - V_j) - I_{ionic,k}$$
\[ g_{\text{Ca}}(V + 70) + [g_{\text{Na}}(P) + g_{\text{K}}(P)](V - 50) +\]
\[ + \sum_{i} g_{i}(V - 50) + g_{\text{K}3}(m_{3}^{C}) + g_{\text{Na}1}(m_{1}^{C}) + g_{\text{Ca}2} + g_{\text{K}4}m_{4}^{C} + g_{\text{K}5}m_{5}^{C} +
\[ + g_{\text{Na}2}(m_{2}^{C}) + g_{\text{K}3}(m_{3}^{C})][V - 95] +\]
\[ + [g_{\text{Na}1}(m_{1}^{C}) + g_{\text{Ca}2} + g_{\text{K}4}m_{4}^{C} + g_{\text{K}3}(m_{3}^{C})][V - 125] + g_{\text{K}4}m_{4}^{C}(V + 35) \]

The evolution of \( m \) and \( h \) variables follows the Hodgkin-Huxley first-order differential equations

\[ \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m; \quad \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \]

Here, \( \alpha_m, \beta_m, \alpha_h, \) and \( \beta_h \) are predefined functions of membrane potential, or—in the case of the AHP conductance—of \( \chi = [\text{Ca}^{2+}] \), the units are ms\(^{-1}\). Note that the density of spikes. Needless to say, the resulting distribution of conductance in the case of the AHP conductance potential, or Ca\(^{2+}\) influx. Thus in each compartment \( \frac{d}{dt} \) assumes to elevate \([\text{Ca}^{2+}] \), in this shell is a signal used, in part, for gating the two.

### Experimental methods

Slices (450-μm-thick) of temporal cortex were obtained from artificial cerebrospinal fluid (ACSF) perfused brains of adult male Wistar rats, anesthetized with isoflurane followed by ketamine/xylazine injection. The animal was perfused once all pain reflexes had disappeared. Slices were maintained in an interface chamber and perfused with artificial cerebrospinal fluid containing the following (in mM): 133 NaCl, 18 NaHCO\(_3\), 3 KCl, 1.25 NaH\(_2\)PO\(_4\), 10 d-glucose, 1 MgCl\(_2\), 1.7 CaCl\(_2\), equilibrated with 95% O\(_2\)-5% CO\(_2\), pH 7.2 at 35°C. Sharp electrode recordings were taken from layer 2/3 pyramidal neurons at the level of soma or apical dendrite.

**SHARP ELECTRODE RECORDINGS.** Membrane potential recordings were obtained from 36 layer 2/3 pyramidal cell somata, 4 fast-spiking (presumed interneuronal) neurons, and 12 presumed dendrites (identified by their characteristic attenuated fast spikes, lack of fast spike AHP, and easy induction of broad bursts of spikes on depolarization). Microelectrodes (resistance 30–90 MΩ) were filled with 1.5 M potassium acetate or potassium methysulfate alone or in conjunction with 0.3 mM of the calcium-chelating agent BAPTA (Sigma, UK). Somatic recordings were examined for evidence of rhythmic bursting activity after long (>10 s) periods of tonic depolarizing current injection (0.5–1.0 nA) (see Brumberg et al. 2000); fast rhythmic bursting was not observed without this depolarization, during experiments with BAPTA. With BAPTA-filled sharp electrode recordings, somatic resting membrane potential (RMP) was \(-68 \pm 4\) mV, and somatic input resistance was \(45 \pm 5\) MΩ. For presumed dendrites, RMP was \(-60 \pm 8\) mV and input resistance was \(62 \pm 4\) MΩ.

Pharmacological manipulation of rhythmic bursting activity was achieved by inclusion, into the extracellular perfusion solution, of the NO source S-nitroso-N-acetylpenicillamine (SNAP) (100 μM, Tocris, UK), to enhance \( g_{\text{Na}P} \) (Hammarstrom and Gage 1999). Phenytoin (120 μM, Sigma) was used to block \( g_{\text{Na}P} \) (Brumberg et al. 2000). Iberiotoxin (IbTx, 50–100 nM, Sigma) was used to block \( g_{\text{K}C} \) (Galvez et al. 1990; Harvey et al. 1995). SNAP effects were manifest over a range of initial incubation times (30 min to 2 h); all data presented were taken after 2-h incubation, for consistency. IbTx effects were seen after 30 min in all cases and lasted for \(\geq 5\) h. In each case, ionotropic glutamate receptor-mediated EPSPs were blocked throughout the experiments, using \( d(-)-2\)-amino-5-phosphono panoic acid, 50 μM (n-AP5) and 2,3-dihydroxy-6-nitro-1,2,3,4-tetrahydrobenz[1]quinoxaline-7-sulfonamide (NBQX, 20 μM), both from Tocris. No prior depolarization steps were required to see rhythmic bursting using either SNAP or IbTx (in contrast to BAPTA).

**RESULTS**

Na\(^{+}\) and Ca\(^{2+}\) electrogenesis in response to dendritic depolarization. Injections of depolarizing current pulses into an apical dendrite of the model evoke either trains of small, fast Na\(^{+}\) action potentials (Fig. 2, left) or else small, fast action potentials that are intermixed with (and superimposed on) slower high-threshold Ca\(^{2+}\)-mediated action potentials (Fig. 2, right). Both of these patterns resemble patterns re-
ported previously in experimental dendritic recordings of layer 2/3 neocortical pyramidal neurons ( Amitai et al. 1993 ) ( and also other types of pyramidal cell, e.g., Kamondi et al. 1989 ). In our model, all of the fast spikes—those that are between and also those that are superimposed on the slow spikes—are initiated perisomatically and backpropagate into the dendrites; this is the case both for tonic intrasomatic and for tonic intradendritic current injections ( data not shown ).

We repeated the simulations of Fig. 2 ( 1.5- or 2.5-nA current pulses into a compartment with a 20-nS shunt) at other locations in the model neuron: just proximal to the site used in Fig. 2, in the mid-apical shaft, and the soma. In these cases, we did not see locally or dendritically generated rhythmic Ca$^{2+}$ spikes. The most likely explanation is that the density of high-threshold Ca$^{2+}$ conductance is high ( in the model ) only at distal dendritic sites ( 3 mS/cm$^2$, Table A1 ), and lower at more proximal and somatic sites. Current pulses at the soma could induce rhythmic bursting ( see also Figs. 4–6 ), but that rhythmic bursting ( unlike Fig. 2, right ) was not associated with dendritic Ca$^{2+}$ spikes: the burst mechanisms are different.

Patterns of fast and slow dendritic action potentials, similar to those of Fig. 2, were elicited in our own experimental recordings, examples of which are shown in Fig. 3A. Interestingly, the slow-action potentials occurred at theta ( 4–12 Hz ) frequencies, while the fast spikes occurred at gamma ( 30–70 Hz ) frequencies, even when slow spikes were also present ( Fig. 3, B and C ). So far as we are aware, the functional significance of the theta frequency slow spikes in neocortical neurons is not known.

**FIG. 4**. Appearance of rhythmic bursting and then fast tonic firing with increasing somatic depolarization: simulation. Increasing somatic depolarizing currents induce bursts of increasing frequency and number of action potentials/burst, and eventually high-frequency tonic firing. $D_{Na_{app}} = 0$, $D_{K_{Ca}} = 1.3$.

In response to increasing somatic depolarization, rhythmic doublets and bursts develop, then rapid tonic firing. The response of the model neuron to somatic depolarizing currents was somewhat different from dendritic depolarizing currents, even when persistent $g_{Na}$ was blocked ( Fig. 4 ). As the current increased, rhythmic firing—which started as single isolated spikes—became associated with spike doublets, and brief bursts, with interburst frequencies at ~20 to ~40 Hz, and within-burst spike intervals ~5 ms ( 1.1 nA ) to ~4–4.5 ms ( 1.5 nA ). Between bursts, there is a hyperpolarization which is mostly generated by $g_{K_{MP}}$, a voltage-dependent K$^+$ conductance, and the K$^+$ conductance of highest density in the model dendrites. [ Recall that in previous experiments ( Brumberg et al. 2000 ), the between-burst hyperpolarizations were “actively generated”. ] Still larger depolarizing currents produced high-frequency tonic firing. The overall pattern of behavior is similar to that reported by Steriade et al. ( 1998 ). [ See also Fig. 3.7 in Steriade ( 2001 ). ]

Figures 5 and 6 provide further information on model behavior, in response to various constant current injections, for two parameter sets. The model neuron in Fig. 5 had no persistent $g_{Na}$, and $g_{K_{Ca}}$ was large. This cell fired rhythmic single spikes over the range of somatic current injections 0.15 to 1.05 nA; firing frequency increased approximately linearly with current amplitude. For larger current injections, however, the model neuron started to fire spike doublets. A 2-s simulation was also run ( not shown ) in which the injected current was ramped slowly from 0.75 to 1.35 nA. Rhythmic single spikes switched to single-spike/spike-doublet pairs at about 1.1
nA, which again switched to just rhythmic doublets at about 1.2 nA.

The model neuron in Fig. 6 had the same large $g_{K(C)}$ as for Fig. 5, but persistent $g_{Na}$ was present ($D_{Na(P)} = 0.7$). This model neuron fired spike doublets over the current range of 0.15 to 0.75 nA (with between-doublet frequency increasing linearly with the stimulus). Larger currents produced relatively little change in doublet or burst frequency, but there were progressively more spikes/burst as the current increased. Within-burst firing frequency for bursts evoked by large currents (e.g., Fig. 6B2) ranged from 250 to 323 Hz.

**PERSISTENT $g_{Na}$ FAVORS FAST RHYTHMIC BURSTING IN THE MODEL.** Other authors have suggested a role of persistent $g_{Na}$ in fast rhythmic bursting based on both theoretical (Wang 1999) and experimental (Brumberg et al. 2000) considerations. In our model also, persistent $g_{Na}$ favors the occurrence of rhythmic bursting, with brief ADPs following the bursts (Fig. 7). (Nevertheless, as will be shown, persistent $g_{Na}$ is not required for fast rhythmic bursting to occur in this model.) The simulations in Fig. 7 show an interesting feature: some of the spike doublets (middle traces) show a spikelet between the two large action potentials (e.g., arrow in Fig. 7B). Similar spikelets were seen in other simulations (not shown), either with tonic current injection or after antidromic stimulation; in these cases, it could be shown (see also Fig. 9) that the somatic spikelet originated as a full axonal spike that was decrementally conducted to the soma and that decremented further with propagation into the dendrites; it could be further shown that during tonic somatic current injection, when the axon was disconnected from the soma, somatic firing could still be induced, but without spikelets (data not shown).

**EXPERIMENTALLY, SNAP INDUCES RHYTHMIC DOUBLETS, SOMETIMES WITH INTERSPERSED SPIKELETS.** Bath application of 100 μM SNAP [a nitric oxide (NO) donor that enhances persistent $g_{Na}$ (Hammarstrom and Gage 1999), 5 experiments] resulted in occasional spontaneous burst discharges at resting membrane potential in all layer II neurons tested after 2 h (RMP = −62 ± 3 mV, $n = 12$). Injection of depolarizing current to maintain membrane potential at −55 mV generated repetitive single spiking in control conditions (spike frequency 14 ± 4 Hz, $n = 12$). After 2-h exposure to SNAP, rhythmic bursting was seen at this membrane potential in 8/12 cells tested (Fig. 8A).

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**FIG. 5.** Current-frequency ($fI$) curve for a model neuron that is rhythmic spiking (RS) over most of the stimulus range. A: $fI$ curve was approximately linear up to a somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$.

**FIG. 6.** $fI$ curve for a model neuron that generates doublets and bursts. A: $fI$ curve was approximately linear up to somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$. **FIG. 7.** $fI$ curve for a model neuron that generates doublets and bursts. A: $fI$ curve was approximately linear up to somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$. **FIG. 8.** $fI$ curve for a model neuron that generates doublets and bursts. A: $fI$ curve was approximately linear up to somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$. **FIG. 9.** $fI$ curve for a model neuron that generates doublets and bursts. A: $fI$ curve was approximately linear up to somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$. **FIG. 10.** $fI$ curve for a model neuron that generates doublets and bursts. A: $fI$ curve was approximately linear up to somatic depolarizing current of 1.05 nA. A 1.2-nA current evoked singlets alternating with doublets, and 1.35- and 1.5-nA currents evoked continuous doublets. B: 2 examples of firing patterns, at points shown in the graph in A. $D_{Na(P)} = 0$, $D_{K(C)} = 1.6$.
Bursting consisted of double spikes occurring at a frequency of 20 ± 5 Hz (n = 8) with an interspike frequency of 224 ± 12 Hz (n = 12). Spike doublets were accompanied by an ADP during rhythmic bursting. No differences were seen in spike widths at half-height for control, single spikes, and the first spike in a burst [control width 0.85 ± 0.05 ms (50 events per n = 12 cells), during rhythmic bursting 0.85 ± 0.7 ms (50 events per n = 8 cells)]. There was also no difference between the widths of the first and second spikes during a burst [second spike width at half-height 0.88 ± 0.06 ms (50 events per n = 8 cells)]. The maximum hyperpolarization following the first spike was significantly reduced when comparing control, single repetitive spikes (–4.5 ± 0.8 mV from the base of the action potential, 50 events per n = 12 cells) with bursts (–3.0 ± 0.2 mV, 50 events per n = 8 cells, P < 0.05).

The ADP was clearly evident in all examples of rhythmic bursting at –55 mV (e.g., see Fig. 8, A and B). Both the ADP and the rhythmic bursting were prevented by bath application of 120 μM phenytoin (Fig. 8B); the effects of phenytoin were reversible after washout (n = 3). However, in the presence of SNAP (phenytoin absent), 4/12 neurons displayed spontaneous bursts of action potentials from RMP that were not accompanied by an ADP (e.g., Fig. 8C). In these cases, both full and partial somatic spikes were evident (e.g., Fig. 8C, *, cf. Fig. 7B). Prevention of somatic spiking by injection of depolarizing current (+0.8 to +1.2 nA) for >10 s, or hyperpolarizing current (–0.2 to –0.5 nA) revealed persisting brief bursts of partial spikes. This suggested a nonsomatic origin for these events. To establish whether these spikes or partial spikes originated in layer II neuronal apical dendrites, we recorded from dendrites in SNAP-bathed slices that showed at least one example of the spontaneous behavior above. Only 3/8 dendrites showed any spontaneous membrane potential transients at RMP (mean = –62 ± 8 mV). These transients took the form of either single dendritic spikes originating from baseline (see Fig. 3), or smaller, brief depolarizations which could occasionally precipitate a single dendritic spike (Fig. 8D). Dendritic spike width at half-height was 4.2 ± 0.8 ms. Mean interspike interval within a burst of partial spikes recorded at the soma was 4.9 ± 1.2 ms (204 Hz), suggesting that the bursts of partial spikes in SNAP do not arise from repetitive dendritic spiking. In addition, even strong depolarization of dendrites did not produce spikes at frequencies faster than about 40 Hz (data not shown).

BURSTS OF SOMATIC SPIKELETS IN SNAP COULD PLAUSIBLY ARISE FROM AXONAL BURSTS. The simulations in Fig. 9 support the idea that SNAP-induced spontaneous runs of somatic spikelets arise in the axon, rather than in dendrites. [The reader will recall that dendritic current injections (Figs. 2 and 3) lead to

![Image](http://jn.physiology.org/)

**Fig. 7.** Increasing persistent $g_{Na}$ favors fast rhythmic bursting:simulation. Simulations were performed with high $g_{K(C)}$ density ($D_{K(C)} = 1.6$). A: as persistent $g_{Na}$ density is increased, the firing pattern evolves from rhythmic single spikes to rhythmic bursting, with increasing numbers of spikes per burst. B: details of action potentials. Note the spikelet in the middle (arrow). In this model, such spikelets originate from extra axonal spikes. [Similar spikelets leading into action potentials were observed by Draguhn et al. (1998) and Schmitz et al. (2001) in low [Ca$^{2+}$] media and were attributed to decremental antidromic invasion.] In addition, in this model (e.g., Fig. 2), tonic stimulation of either soma, or of dendrites themselves, leads to spike initiation in the axon, not in the dendrites.

![Image](http://jn.physiology.org/)

**Fig. 8.** The NO donor S-nitroso-N-acetylpenicillamine (SNAP, 100 μM) induces fast rhythmic bursting that is suppressed by phenytoin and that is associated with spikelets that appear to derive from axons. A: example 1-s traces from layer 2 temporal neocortical neuron. **Top:** pattern of repetitive firing when this neuron was depolarized to an average membrane potential of –55 mV. **Bottom:** repetitive burst firing in the same neuron 2 h after addition of SNAP (100 μM) to the bathing medium. Bursting occurred spontaneously at resting membrane potential (–62 mV in this case), but example shows the pattern of activity at –55 mV for comparison with control. **B:** multiple spikes in the presence of SNAP are generated by an afterdepolarization (ADP) compared with control. Both bursting and the ADP were abolished by bath application of 120 μM phenytoin. **C:** in the presence of SNAP (phenytoin absent), spontaneous bursts at resting membrane potentials were often associated with partial spikes. Injection of strong depolarizing current into the cell soma through the recording electrode abolished full spikes but brief trains of partial spikes remained (**top** trace). Similarly, hyperpolarization to –90 mV abolished full spikes, while leaving brief trains of partial spikes. **D:** during spontaneous bursting induced by SNAP, dendritic recordings show brief depolarizations, without either full or partial spikes. Injection of +0.1-nA current induced single dendritic spikes on the peak of the depolarizations, but not bursts. The dendritic spikes, when they occurred, were broader than even pairs of spikelets recorded at the soma, suggesting that somatic spikelets were not initiated 1:1 by dendritic spikes. (Phenytoin was absent in this experiment.)
spikelets. If the soma was not too hyperpolarized (Fig. 9 [Draguhn et al. 1998], axonal spike trains produced somatic expected from similar simulations of CA3 pyramidal cells model axon, producing brief fast trains of axonal spikes. As spikelets.

In Fig. 9, we injected small current pulses into the B ciently hyperpolarized (Fig. 9 C or more full somatic spikes could occur as well (cf. Fig. 8 A).

FIG . 9. Spontaneous runs of somatic spikelets (as in Fig. 8C) could, in principle, result from axonal spike bursts:simulation. A: an 18-ms current pulse was passed into the distal axon when the soma was at $-70 \text{ mV}$. The resulting burst of axonal action potentials leads to a somatic spike, a large spikelet, and a run of smaller spikelets. A broad attenuated action potential is induced in an apical branch compartment (just past the 2nd branch point), resembling the dendritic potential in Fig. 8D. B: application of the same current stimulus when the soma was at $-85 \text{ mV}$ led to fewer axonal spikes, and only spikelets at the soma. The dendrite displays only a slow potential with superimposed rippling. $D_{\text{Na}(P)} = 1.0, D_{\text{K(C)}} = 1.0$.

dendritic spikelets, but not—in the model at least—to somatic spikelets.] In Fig. 9, we injected small current pulses into the model axon, producing brief fast trains of axonal spikes. As expected from similar simulations of CA3 pyramidal cells (Draguhn et al. 1998), axonal spike trains produced somatic spikelets. If the soma was not too hyperpolarized (Fig. 9A), one or more full somatic spikes could occur as well (cf. Fig. 8C); full somatic spikes did not occur when the soma was sufficiently hyperpolarized (Fig. 9B, cf. Fig. 8C). The backpropagating somatic spike in Fig. 9A led to a broadened, attenuated dendritic spike, resembling the experimental dendritic spike of Fig. 8D.

Draguhn et al. (1998) showed that model somatic/dendritic K+ conductances influence axonal invasion of the soma. Experimentally, Schmitz et al. (2001) showed that somatic membrane potential and Na+ channel inactivation influence the invasion. In the present model (data not shown), $g_{\text{Na}(P)}$ also influences spike invasion from the axon. For example, if the simulation of Fig. 9A is repeated with a 50% increase in $g_{\text{Na}(P)}$ density, and all other parameters remain the same, then four full somatic spikes occur, instead of just one.

AXONAL SPIKES CAN, IN PRINCIPLE, LEAD TO SPIKE ADPS. The simulation of Fig. 10 shows that an axonal spike can, in principle, lead to a spike ADP, even without persistent $g_{\text{Na}}$. This phenomenon could contribute to the relatively sharp spike ADPs that are sometimes shown in the literature, in neurons capable of FRB (e.g., Fig. 3B1 in Steriade 2001).

BLOCKING $g_{\text{Ca}}$ FAVORS SPIKE DOUBLETS AND FAST RHYTHMIC BURSTING. Both Brumberg et al. (2000) and Nishimura et al. (2001) used ionic manipulations to show that blocking $g_{\text{Ca}}$ not only fails to suppress rhythmic bursting, but may even enhance it. In our model as well (data not shown), progressive blockade of $g_{\text{Ca}}$ converted rhythmic single action potentials to rhythmic doublets, and then to rhythmic bursts. These simulations were done without persistent $g_{\text{Na}}$, and with a relatively high-density of $g_{\text{K(C)}} (D_{\text{Na}(P)} = 0, D_{\text{K(C)}} = 1.6)$.

These results serve to emphasize that, even though the dendrites of layer 2/3 neocortical neurons can generate rhythmic slow (presumably Ca$^{2+}$-mediated) action potentials (Figs. 2 and 3), such slow action potentials are probably not required for fast rhythmic bursting.

REDUCING INTRACELLULAR [Ca$^{2+}$] FAVORS SPIKE DOUBLETS AND FAST RHYTHMIC BURSTING. We also performed simulations in which a fixed ceiling was imposed on [Ca$^{2+}$], whose units, in the model, are arbitrary (see METHODS). As this ceiling was reduced during repeated injections of the same depolarizing current pulse (data not shown), first rhythmic doublets appeared, and then rhythmic bursts. Similar behavior was observed experimentally (data not shown) as BAPTA (0.3 mM) entered a layer 2/3 neuron from the recording electrode—although BAPTA acts as a buffer of [Ca$^{2+}$], rather than imposing an exact ceiling. BAPTA induced rhythmic bursting in all regular spiking cells tested ($n = 10$). The mean interspike

FIG . 10. A fast spike ADP can be generated primarily in the axon, without requiring persistent $g_{\text{Na}}$ simulation. The model neuron was stimulated antidromically, with a current pulse to a distal axonal compartment. The broad somatic spike (i.e., broad relative to an axonal spike) re-excites the axon, generating a “reflected” spike (as shown to occur experimentally in CA3 hippocampal pyramidal neurons; Traub et al. 1994). The reflected axonal spike induces a brief spike ADP in the soma (arrow) [cf. Figs. 7 and 8, and also Brumberg et al. (2000) (their Fig. 3A)]. The somatic spike ADP is not generated in the apical dendrite: the spike ADP in the distal apical shaft is smaller, slower, and peaks later than the somatic ADP, i.e., the dendritic spike ADP is backpropagated. Persistent Na+ conductance is absent in this simulation. $D_{\text{Na}(P)} = 0.7, D_{\text{K(C)}} = 1.6$. 
interval during bursts induced in this way was 5 ± 1 ms, and burst frequency was 12–24 Hz. Friedman and Gutnick (1989) had previously shown a pair of bursts in a neocortical neuron injected with EGTA. None of four fast-spiking neurons developed fast rhythmic bursting on BAPTA injection.

REDDUCING $g_{K(C)}$ FAVORS SPIKE DOUBLETS AND FAST RHYTHMIC BURSTING. The fact that bursting, in the model and in real cells becomes more intense with $g_{Ca}$ reduction, or with intracellular [Ca$^{2+}$] reduction, suggests that it is suppression of one or more Ca$^{2+}$-gated K$^+$ conductances that underlies fast rhythmic bursting, at least under some conditions. But which one(s)? We were not able to induce fast rhythmic bursting in regular-spiking model neurons solely by manipulation of the slow AHP conductance, $g_{K(AHP)}$ (data not shown). On the other hand, simulated reductions of the fast voltage- and Ca$^{2+}$-gated conductance $g_{K(C)}$ (Kang et al. 1996)—which is fast enough to contribute to action potential repolarization in hippocampal pyramidal neurons (Shao et al. 1999)—did lead to a transition from rhythmic spike to fast rhythmic bursting (Fig. 11A), in a pattern similar to that seen with reduction of $g_{Ca}$, or with reduction of intracellular [Ca$^{2+}$]. Spikelets were sometimes observed during the course of simulated bursts induced by reduction of $g_{K(C)}$.

Experimentally as well, IbTx (which blocks the BK channels that mediate $g_{K(C)}$), induces fast rhythmic bursting. Bath application of 50 nM IbTx transformed repetitive spiking at a membrane potential of −55 mV into rhythmic bursting in all cells tested ($n = 6$) (Fig. 11B). Burst frequency was 17 ± 4 Hz with a within-burst spike frequency of 170 ± 14 Hz. Differences in the profile of spike bursts were seen between rhythmic bursting generated by IbTx and SNAP (see Fig. 8B). In both cases multiple spikes were accompanied by an ADP, but with IbTx the postspike hyperpolarization was less evident, and both first and second spikes in a burst were prolonged compared with controls. Control initial afterhyperpolarization was $-4.2 \pm 0.8$ mV from the base of the action potential, but this changed to $+0.6 \pm 1.0$ mV in the presence of IbTx. Control repetitive spiking consisted of action potentials with a width at half-height of 0.9 ± 0.2 ms and this was prolonged during rhythmic bursting to 1.4 ± 0.3 ms. The second spike in a burst was further prolonged with a width at half-height of 1.8 ± 0.3 ms. It is interesting that Brumberg et al. (2000) noted a prolongation of spike width, as rhythmic spiking (RS) cells converted to FRB cells following prolonged current injection.

The above pattern of changes in action potential profile was not seen during repetitive bursting with SNAP. In addition, IbTx-induced repetitive bursting was insensitive to 1-h application of 120 μM phenytoin (Fig. 11, C and D), which neither prevented bursting nor altered IbTx-induced changes in action potential profile or ADP ($n = 3$ experiments). This suggested a different mechanism for burst generation in IbTx, unrelated to enhanced $g_{Na(DP)}$. We tested whether these two mechanisms (enhanced $g_{Na(DP)}$ versus reduced $g_{K(C)}$) could be cooperative by inducing rhythmic burst firing by bath application of both SNAP (100 μM) and IbTx ($n = 3$). In this case, tonic depolarization to −55 mV induced a slower pattern of bursting (15 ± 3 Hz) with a greater number of spikes within each burst (range = 2–6 spikes) (Fig. 11B, bottom). Within-burst spike frequency was approximately the same as before (140–230 Hz). There was no significant difference in burst frequency when comparing SNAP + IbTx with either SNAP alone, or with IbTx alone (20 ± 5 and 17 ± 4 Hz, $P > 0.05$). There was, however, a significant increase in the median number of spikes per burst [SNAP alone = 2 (interquartile range, IQR, 1–3), IbTx alone = 2 (IQR 1–3), SNAP + IbTx = 4 (IQR 2–6), $P < 0.05$].

DURING THE COURSE OF A BURST, SOMATIC SPIKES DEVELOP INCREASING INFLECTIONS ON THEIR UPSTROKES (AS ALSO SHOWN BY BRUMBERG ET AL. (2000), THEIR FIG. 11A). The data so far suggest that fast membrane processes, on a few-millisecond time scale, are critical in allowing fast rhythmic bursting to occur. Such fast processes suggest involvement of the axon in this unique firing behavior. We noted in simulations that the very fast $g_{Na}$ and $g_{K(DR)}$ used in this model led to a high degree of axonal excitability. The distal axon, for example, would fire two spikes on occasion to the soma’s single spike (e.g., Figs. 9 and 10); or, during somatic spike triplets, the axon might fire five times (data not shown). Some simulations (e.g., Fig. 7B) showed spikelets and notched action potentials (cf. Draguhn et al. 1998; Schmitz et al. 2001), and spikelets could also be observed in experimental recordings (e.g., Fig. 8C). It was therefore interesting to notice—both in simulations and in confirmatory experiments (cf. Brumberg et al. 2000)—that the upstrokes of somatic action potentials became progressively more inflected during the course of a burst, consistent with axonal initiation of the spikes (data not shown). This axonal
initiation was directly confirmed in simulations. The progressively increasing somatic spike inflections probably result from increasing soma/dendritic K\(^+\) conductances and Na\(^+\) channel inactivation that develop during the burst.

**DISCUSSION**

Intrinsic oscillatory properties at gamma frequency, both subthreshold and chattering, in neocortical neurons have been suggested to be important in the generation of network gamma oscillations in the cortex (Gray and McCormick 1996; Llinás et al. 1991; Nuñez et al. 1992; Steriade et al. 1998). For this reason alone, an understanding of the cellular mechanisms is essential. Understanding of cellular mechanisms—specifically, which currents are involved in producing particular firing behaviors—is additionally important, because such understanding allows one to make predictions as to how the currents (and thus the firing behaviors) might be regulated by the brain in vivo. It is noteworthy, for example, that persistent Na\(^+\) conductance can be influenced by NO (Hammarstrom and Gage 1999), while BK channels are regulated by protein kinase A (Dvoretsky et al. 1996). Here, we have concentrated on fast rhythmic bursting—firing patterns of full action potentials that decrement only slightly in amplitude—rather than on subthreshold behavior.

We have constructed a multi-compartment, multi-conductance model of a layer 2/3 neocortical neuron that uses voltage-clamp kinetic data for simulating many of the channel types (e.g., Martina et al. 1997). Dendritic electrogenesis in this model looks reasonably realistic (Figs. 2 and 3). Contrary to our expectations when building this model (which was not originally intended to simulate fast rhythmic bursting), the model did indeed produce fast rhythmic bursting of a form similar to that seen in vivo (Steriade et al. 1998). In addition, the model agrees well with experimental data on rhythmic doublets and bursts, obtained from adult rat neocortical slices with sharp electrodes. It therefore makes sense to examine the predictions made by, and interpretations suggested by, this model as to the cellular mechanisms of fast rhythmic bursting.

What the model suggests is that one important set of membrane properties contributing to fast rhythmic bursting may be the kinetics of fast Na\(^+\) and fast K\(^+\) channels, especially in the axon. These properties alone (data not shown) allow spike ADPs to occur, when the axonal membrane is depolarized, and promote a ready tendency to produce spike multiplets. Persistent \(g_{Na}\) contributes to this tendency, not only because of its limited (in the model, nonexistent) inactivation, but also because of its relatively low activation threshold (French et al. 1990; Kay et al. 1998). Experimental data reported here [as well as previously (Brumberg et al. 2000)] are also consistent with a role for persistent \(g_{Na}\) in fast rhythmic bursting. In addition, the tendency for axonal spike multiplets to invade the soma could be regulated, we suggest, in part by \(g_{K(C)}\), a fast voltage- and calcium-gated conductance. \(g_{K(C)}\) is likely present in soma and dendrites (Kang et al. 1996); the fact that \(g_{Ca}\) is present in Purkinje cell axons (Calweerta et al. 1996) makes it conceivable that \(g_{K(C)}\) is present in axons as well, although we did not include axonol \(g_{K(C)}\) in the model. In the model, reduction of soma/dendritic \(g_{K(C)}\) could induce fast rhythmic bursting (in response to depolarizing stimuli) even in the absence of persistent \(g_{Na}\), as could reducing calcium entry or intracellular calcium concentration. Dendritic depolarizations do not appear to contribute in a significant way, at least in the model. Experimentally, bath application of the BK channel blocker (i.e., \(g_{K(C)}\) blocker) IbTx also induced fast rhythmic bursting that is resistant to phentoin, both as the model predicts. Presumably, the toxin is acting uniformly on somatic, dendritic, and axonal (if such exist) locations of BK channels.

Both in the model and in the experiment, fast rhythmic bursting could be accompanied by somatic spikes that did not originate in apical dendrites and that (in the model, at least) could be shown to originate in the axon. These observations are also consistent with the hypothesis that axonal excitability contributes to fast rhythmic bursting.

In the model, it is additionally important that there be a voltage-dependent (and calcium-independent) K\(^+\) conductance, of relatively large amplitude and appropriate kinetics, to regulate the interburst interval. In our simulations, this role is played by \(g_{K(M)}\) but we have no experimental data concerning the presence or absence of cholinergic regulation of this conductance; if no cholinergic regulation turns out to be present, it does not influence the basic ideas of the model, provided the conductance has appropriate amplitude and kinetics.

Intraburst intervals, both in model and in experiments reported here, are often not as short as those seen in other in vitro preparations (e.g., Brumberg et al. 2000) or in vivo (Gray and McCormick 1996; Steriade et al. 1998). The reasons for this are not clear. One possibility in vivo is that chattering occurs in the presence of metabotropic activation that would tend to reduce leak (and other) K\(^+\) conductances. In addition, both our (isolated) model neurons and experimentally recorded neurons rarely burst at frequencies over 30 Hz. It should be emphasized, however, that previously reported chattering cells may—in response to current injections—discharge bursts in the 10–30 Hz range (e.g., Figure 3F of Gray and McCormick 1996). Because of the limited intraburst firing frequencies in our data, however, it is appropriate to remain cautious as to how, or if, our data apply to chattering in vivo.

If fast rhythmic bursting is of importance for in vivo gamma rhythms, one expects that the intrinsic oscillation could be gated by inhibitory postsynaptic potentials (IPSPs), as well as by intracellular depolarization: such gating is characteristic of virtually all in vitro network gamma rhythms (Fisahn et al. 1998; Whittington et al. 1995, 1997); it is not apparent how tight network synchrony could occur without regulation by IPSPs (reviewed in Traub et al. 1999). If it is additionally true that axonal properties are critical for chattering to occur, as we suggest, then axo-axonic inhibitory neurons would be expected to play an important role in network gamma oscillations. Preliminary simulations have been performed with a network of RS, FRB, fast-spiking (FS) interneurons, and low-threshold spiking (LTS) interneurons (Gibson et al. 1999). In the simulations, some FS interneurons inhibit principal cell axon initial segments, while others inhibit somata and proximal dendrites; the LTS interneurons inhibited dendrites. These simulations confirm that model FRB cells can participate in synchronized gamma oscillations at frequencies ≈50 Hz.
APPENDIX

Further model parameters

<table>
<thead>
<tr>
<th>Conductance Type</th>
<th>Axon</th>
<th>Soma</th>
<th>Dendrites</th>
</tr>
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<tbody>
<tr>
<td>$g_{Na}$-transient</td>
<td>400</td>
<td>187.5</td>
<td>125 &amp; 93.75 (proximal), 6.25</td>
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<tr>
<td>$g_{Na}$-persistent</td>
<td>0</td>
<td>0</td>
<td>$D_{Na,P} \times 0.0032 \times \text{transient value}$</td>
</tr>
<tr>
<td>$g_{K}$-delayed rectifier</td>
<td>400</td>
<td>125</td>
<td>93.75 proximal, 0 distal</td>
</tr>
<tr>
<td>$g_{K}$-transient (&quot;A&quot;)</td>
<td>2</td>
<td>30</td>
<td>30 apical shaft, 2 elsewhere</td>
</tr>
<tr>
<td>$g_{Ca}$-low-threshold</td>
<td>0</td>
<td>0</td>
<td>$D_{Ca,L} \times 12 \text{ soma &amp; proximal, elsewhere}$</td>
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<tr>
<td>$g_{K}$-AHP</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
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<td>$g_{K}$&quot;K2&quot;</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>$g_{K}$&quot;M&quot;</td>
<td>0</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>$g_{Ca}$-low-threshold</td>
<td>0</td>
<td>0.5</td>
<td>0.5, except 3.0 distal 3 levels</td>
</tr>
<tr>
<td>Anomalous rectifier</td>
<td>0</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conductance Type</th>
<th>Activation/Inactivation</th>
<th>Time Constant (ms)</th>
</tr>
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<tbody>
<tr>
<td>$g_{Na}$-transient: activation</td>
<td>$1/[1 + \exp((-V - 34.5)/10)]$;</td>
<td>0.025 + 0.14 $\exp([-V - 26.5]/10) [V \leq -26.5]$</td>
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<tr>
<td>$g_{Na}$-transient: inactivation</td>
<td>$1/[1 + \exp([V + 59.4]/10.7)]$;</td>
<td>0.02 + 0.14 $\exp([-V - 26.5]/10) [V \leq -26.5]$</td>
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<tr>
<td>$g_{Na}$-persistent: activation</td>
<td>$1/[1 + \exp((-V - 48)/10)]$;</td>
<td>0.15 + 1.15 $\exp([V + 33.5]/15])$</td>
</tr>
<tr>
<td>$g_{Ca}$-low-threshold: activation</td>
<td>$1/[1 + \exp((-V - 29.5)/10)]$;</td>
<td>0.025 + 0.14 $\exp([V + 40]/10) [V \leq -40]$</td>
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<tr>
<td>$g_{K}$&quot;AHP&quot;</td>
<td>$1/[1 + \exp((-V - 60)/8.5)]$;</td>
<td>0.25 + 4.35 $\exp([V + 10]/10) [V \leq -10]$</td>
</tr>
<tr>
<td>$g_{K}$&quot;M&quot;</td>
<td>$1/[1 + \exp((V + 78)/6)]$;</td>
<td>0.25 + 4.35 $\exp([V - 10]/10) [V \geq 10]$</td>
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<tr>
<td>$g_{Ca}$-high-threshold: activation</td>
<td>$1/[1 + \exp((V + 80)/4)]$;</td>
<td>0.185 + 0.5 $\exp([V + 35.8]/19.7) + \exp([-V - 79.7]/12.7)]$</td>
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<tr>
<td>Anomalous rectifier</td>
<td>$1/[1 + \exp((V + 75)/5.5)]$;</td>
<td>0.5 $\exp([V + 46.5]) + \exp([-V - 238]/37.5]$</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Conductance Type</th>
<th>Forward Rate Function ($\alpha$)</th>
<th>Backward Rate Function ($\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Ca}$-&amp; $V$-dependent (&quot;C&quot;)</td>
<td>0.03 $\exp([V + 50]/11 - (V + 53.5)/27]$</td>
<td>2 $\exp((V - 53.5)/27) - \alpha$</td>
</tr>
<tr>
<td>(voltage-dependent term)</td>
<td>$[V \leq -10]$</td>
<td>$[V \leq -10]$</td>
</tr>
<tr>
<td></td>
<td>2 $\exp([-V - 53.5]/27)$</td>
<td>0 $[V \leq -10]$</td>
</tr>
<tr>
<td></td>
<td>$[V \geq -10]$</td>
<td>$[V \geq -10]$</td>
</tr>
<tr>
<td>$g_{K}$&quot;M&quot;</td>
<td>0.02 $[1 + \exp([-V - 20.5]/5)]$;</td>
<td>0.01 $\exp([-V - 43]/18)$</td>
</tr>
<tr>
<td>$g_{K}$&quot;AHP&quot;</td>
<td>$\min(10 \cdot \chi, 0.01)$;</td>
<td>0.01</td>
</tr>
<tr>
<td>$g_{Ca}$-high-threshold:</td>
<td>1.6 $[1 + \exp((-0.072)(V - 5))]$;</td>
<td>0.02 ($V + 8.9)/[\exp([V + 8.9]/5) - 1]$</td>
</tr>
</tbody>
</table>

Kinetic data are for activation, unless specified otherwise. Membrane potential, $V$, in mV. [Ca]-dependence of “C” and AHP conductances are described in METHODS, as is description of [Ca] dynamics. “$\chi$” designates [Ca], units arbitrary.
We thank A. Bibbig for helpful discussions, and M. Steriade for discussions and encouragement. This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-44133-01 to R. D. Traub, the Wellcome Trust, and the Medical Research Council (United Kingdom).

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