Dendritic Voltage-Gated Ion Channels Regulate the Action Potential Firing Mode of Hippocampal CA1 Pyramidal Neurons

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Magee, Jeffrey C. and Michael Carruth. Dendritic voltage-gated ion channels regulate the action potential firing mode of hippocampal CA1 pyramidal neurons. J. Neurophysiol. 82: 1895–1901, 1999. The role of dendritic voltage-gated ion channels in the generation of action potential bursting was investigated using whole cell patch-clamp recordings from the soma and dendrites of CA1 pyramidal neurons located in hippocampal slices of adult rats. Under control conditions somatic current injections evoked single action potentials that were associated with an after-hyperpolarization (AHP). After localized application of 4-aminopyridine (4-AP) to the distal apical dendritic arborization, the same current injections resulted in the generation of an afterdepolarization (ADP) and multiple action potentials. This burst firing was not observed after localized application of 4-AP to the soma/proximal dendrites. The dendritic 4-AP application allowed large-amplitude Na+-dependent action potentials, which were prolonged in duration, to backpropagate into the distal apical dendrites. No change in action potential backpropagation was seen with proximal 4-AP application. Both the ADP and action potential bursting could be inhibited by the bath application of nonspecific concentrations of divalent Ca2+ channel blockers (NiCl and CdCl). Ca2+ channel blockade also reduced the dendritic action potential duration without significantly affecting spike amplitude. Low concentrations of TTX (10–50 nM) also reduced the ability of the CA1 neurons to fire in the bursting mode. This effect was found to be the result of an inhibition of backpropagating dendritic action potentials and could be overcome through the coordinated injection of transient, large-amplitude depolarizing current into the dendrite. Dendritic current injections were able to restore the burst firing mode (represented as a large ADP) even in the presence of high concentrations of TTX (300–500 μM). These data suggest the role of dendritic Na+ channels in bursting is to allow somatic/axonal action potentials to backpropagate into the dendrites where they then activate dendritic Ca2+ channels. Although it appears that most Ca2+ channel subtypes are important in burst generation, blockade of T- and R-type Ca2+ channels by NiCl (75 μM) inhibited action potential bursting to a greater extent than L-channel (10 μM nifedipine) or N-, P/Q-type (1 μM omega-conotoxin MVIIIC) Ca2+ channel blockade. This suggests the Ni-sensitive voltage-gated Ca2+ channels have the most important role in action potential burst generation. In summary, these data suggest that the activation of dendritic voltage-gated Ca2+ channels, by large-amplitude backpropagating spikes, provides a prolonged inward current that is capable of generating an ADP and burst of multiple action potentials in the soma of CA1 pyramidal neurons. Dendritic voltage-gated ion channels profoundly regulate the processing and storage of incoming information in CA1 pyramidal neurons by modulating the action potential firing mode from single spiking to burst firing.

INTRODUCTION

Under normal, in vivo, conditions hippocampal pyramidal neurons fire either single action potentials or high-frequency bursts of multiple action potentials (Kandel and Spencer 1961; Ranck and Feder 1973; Pavlides and Winson 1989; Ylinen et al. 1995). These are two fundamentally different modes of firing, and a change from one mode to the other can drastically alter the processing of incoming signals. There is, in fact, evidence that action potential bursts are more important units of information than single action potentials (reviewed in Lisman 1997). In support of this concept, it has been observed that the types of computations performed by many neurons are most accurately represented when only the bursts of action potentials are considered (Otto et al. 1991). This information-rich aspect of burst firing also has been hypothesized to be important in the consolidation of new memories, a process in which the hippocampus is known to be required (Buzsaki 1989; Cattaneo et al. 1981). Burst firing in the hippocampus is, therefore, important in both the processing and storage of neuronal information.

The mechanisms by which hippocampal CA1 pyramidal neurons generate bursts of action potentials are still incompletely characterized. Most studies agree that the generation of an afterdepolarization (ADP) provides the prolonged somatic depolarization required for the initiation of multiple spikes (Jensen et al. 1994, 1996; White et al. 1989; Wong and Prince 1981). There is, however, some discrepancy about the ionic mechanisms underlying this ADP with some studies suggesting that a persistent Na+ current may be involved (Azouz et al. 1996), whereas others have suggested that Ca2+ currents are most important (Andreasen and Lambert 1995; Hoffman et al. 1997; Traub et al. 1993; White et al. 1989; Wong and Prince 1981). There is also considerable evidence that the active membrane properties of the dendritic arborization are involved in the generation of ADPs and action potential bursting (Andreasen and Lambert 1995; Hoffman et al. 1997; Traub et al. 1993; Wong and Stewart 1992; Wong et al. 1979). Therefore, the voltage-gated ion channels located in the dendritic arborizations of CA1 pyramidal neurons may be responsible for modulating the mode of action potential firing in these cells.

At the present time the dendrites of CA1 pyramidal neurons have been shown to contain Na+, Ca2+, K+, and H-currents (Hoffman et al. 1997; Kavalali et al. 1997; Magee 1998; Magee and Johnston 1995; Mickus et al. 1999; Tsubakawa et al. 1999). One current in particular, a transient outward, A-type, K+ current, tends to dominate the regenerative active properties of the dendrites and in turn the entire cell itself (Hoffman et al. 1997). The density of this current increases nearly fivefold from the soma to 350 μm out into the apical dendrites and as a result the more distal dendrites are only weakly excitable under control, in vitro, conditions (Hoffman et al. 1997; Magee...
et al. 1998). The activity of the dendritic A-type K⁺ channels, and their likely molecular correlate Kᵥ4.2, are highly modulatable through numerous mechanisms (e.g., neuromodulatory substances, specific subunit composition, and membrane potential) (see Hoffman and Johnston 1998; Magee et al. 1997). Because of these characteristics, the A-type K⁺ channel population located in the dendrites appears to be well suited to the task of regulating the firing mode of CA1 pyramidal neurons.

To investigate the role of dendritic voltage-gated ion channels in the generation of action potential bursting, we have used whole cell patch-clamp recordings from the soma and dendrites of CA1 pyramidal neurons located in hippocampal slices of adult rats. We report here that a reduction in the amplitudes of backpropagating action potentials and the subsequent dendritic-initiation of Ca²⁺-dependent potentials (see also Hoffman et al. 1997). The dendritic Ca²⁺-potentials then provide the prolonged inward current required for the generation of the ADP and action potential bursting. The role of backpropagating action potentials and the specific Ca²⁺-channel subtypes involved also were explored.

**Methods**

**Preparation**

Hippocampal slices (400 μm) were prepared from 6- to 12-wk-old Sprague-Dawley rats using standard procedures that have been described previously (Magee 1998). Individual neurons were visualized with a Zeiss Axioskop fit with differential interference contrast (DIC) optics using infrared illumination. All neurons exhibited resting membrane potentials between ~60 and ~75 mV. Area CA3 was removed surgically from each slice just before use.

**Recordings and solutions**

Whole cell patch-clamp recordings were made using two Dagan BVC-700 amplifiers (Minneapolis, MN) in active “bridge” mode. Data was acquired (10–20 kHz, filtered at 1kHz) using an Instutute ITC-16 interface (Great Neck, NY) and Pulse Control software (Richard Bookman, University of Miami) written for Igor Pro (Wavemetrics, Lake Oswego, OR). External solutions contained (in mM): 125 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 25 NaHCO₃, 2.0 CaCl₂, 1.25 NaH₂PO₄, 2.5 dextrose, and 0.01 6,7-dinitroquinoxaline 2,3-bis(1,4-h)-dione (DNQX). The solution was bubbled with 95% O₂-5% CO₂ at 37°C. Series resistance for somatic recordings was always <2 MΩ, and for dendritic recordings was 6–20 MΩ.

**Drug preparation and application**

Drug containing perfusion solutions were the same as the external solution with the 25 mM NaHCO₃ replaced by 10 mM HEPES and 10 mM 4-AP. Final concentrations of TTX (10–50 nM), ω-conotoxin MVIIC (1 μM), NiCl₂ (750 or 75 μM), CdCl₂ (500–750 μM), and nimodipine (10 μM) were achieved by mixing stock solutions with either the standard external or perfusion external solution. Nimodipine was dissolved in DMSO (final DMSO concentration was 0.1%), whereas all others were dissolved in water to make stock solutions. Because of the light sensitivity of nimodipine, it was used under dark conditions.

We used a pressure ejection system composed of a computer controlled pneumatic pump (Medical Systems, Greenvale, NY) connected to a somatic patch pipette to locally apply 10 mM 4-AP. The pressures (10–20 psi) and durations (5–8 s) required to perfuse an ~200-μm-diam region of the cell were tested using fluorescent dyes (Lucifer yellow or cascade blue). With such settings, a distal region of the cell (~150–350 μm from the soma) could be perfused when the pipette was placed within 20 μm of the dendritic trunk ~250 μm from the soma. When the pipette was placed at a proximal point on the apical trunk (~<50 μm from the soma), a proximal region (proximal 150 μm of the apical dendrite, the soma and ~50 μm of the proximal basal dendrite) of the cell could be perfused.

**Data analysis**

The amount of bursting was quantified by determining the ADP duration and the number of spikes generated during the ADP (for 30 s after 4-AP application). ADP duration was measured after the termination of the current injection as the time the potential stayed above one-half of spike threshold (see Fig. 1B). Traces occurring 30 s after 4-AP application (15 sweeps given at 2-s intervals) were averaged, and the ADP was measured from this average trace. The number of spikes fired was the total number of action potentials occurring during the ADP for 30 s after the application of 4-AP (15 total current injections given at 2-s intervals). ANOVA and Fishers post hoc test were performed to test for statistical significance.

**Results**

**Role of dendritic K⁺ channels in bursting**

It has been shown previously that bath application of millimolar concentrations of 4-AP causes burst and repetitive action potential firing in CA1 pyramidal neurons (Andreasen and Lambert 1995; Hoffman et al. 1997). To test the role of distal, as opposed to proximal, K⁺ channels in the regulation of burst firing, 4-AP was applied via a perfusion pipette to either the distal apical dendritic trunk (~250 μm) or to a proximal location (~<50 μm; Fig. 1A). Under control conditions, somatic current injections (20 ms, 400–800 pA) were given to CA1 pyramidal neurons to evoke a single action potential during each injection period. With distal 4-AP application, the 20-ms-long current injections evoked bursts of multiple action potentials (usually 3 or 4 but =8 could be initiated) that generally increased in amplitude during the burst. No such effect was elicited by proximal application of 4-AP (Fig. 1). The distal current injection caused a pronounced ADP which appeared as a “hump” in the somatic membrane potential after the current injection. The average duration of the ADP (at half threshold) and the total number of spikes fired (for 30 s after application) was much longer for distal application (41 ± 3 ms, 5 ± 0.5 action potentials, n = 31) than for proximal application (18 ± 6 ms, 0 action potentials, n = 5) or with no application (16 ± 2 ms, 0 action potentials, n = 31; Fig. 1, B and C). The 4-AP-sensitive K⁺ channels located within the distal dendritic arbor of CA1 pyramidal neurons are therefore capable of controlling the firing mode (single spiking or burst firing) of these cells.

By what mechanisms do these distal channels regulate the firing mode of the entire cell? Simultaneous dendritic and somatic voltage recordings from a separate population of neurons revealed that the amplitude and duration of the backpropa-
The ADP likewise was reduced by high concentrations of Cd$^{2+}$ or Ni$^{2+}$, indicating that it is generated by the inward current carried by dendritic voltage-gated Ca$^{2+}$ channels (4-AP: 48 $\pm$ 7 ms; 4-AP and divalents: 22 $\pm$ 7 ms; $n$ = 4). Together these data indicate that dendritic action potentials are capable of evoking a substantial Ca$^{2+}$ influx through voltage-gated Ca$^{2+}$ channels once they are released from the shunting effect of distal dendritic K$^+$ channels. This Ca$^{2+}$ current propogates to the soma to generate the somatic ADP that is responsible for the induction of burst firing. Such events were not observed when the proximal K$^+$ channel population was reduced. The distal dendritic K$^+$ channels, therefore appear to regulate burst firing in CA1 pyramidal neurons by modulating the backpropagation of dendritic action potentials.

**Role of backpropagating action potentials in bursting**

It has been reported previously that low concentrations of TTX are capable of blocking burst firing in CA1 pyramidal neurons without affecting somatic spike amplitude (Azouz et al. 1996). Because of the low safety factor of dendritic action potential propagation, low concentrations of TTX also have been shown to greatly inhibit the backpropagation of action potentials into the dendrites (Mackenzie and Murphy 1998; Magee and Johnston 1997). We therefore sought to test the hypothesis that low concentrations of TTX can inhibit burst firing by reducing the amplitude of dendritic action potentials and associated Ca$^{2+}$ current.

Low TTX concentrations were applied to the slice either by bath perfusion of 10 nM TTX or by including 50 nM TTX along with 4-AP in the perfusion pipette. Both methods were equally effective in inhibiting action potential bursting that was induced by distal 4-AP application ($43 \pm 3$ vs. $26 \pm 6$ ms ADP, $5 \pm 0.5$ vs. $1 \pm 1$ action potentials, $n$ = 6), without significantly affecting somatic action potential amplitude ($94 \pm 4$ vs. $90 \pm 5$ mV).

Simultaneous somatic and dendritic recordings in another set of neurons show that bath application of 10 nM TTX reduced the amplitude of the dendritic spike from 76 $\pm$ 7 to 21 $\pm$ 7 mV (with 4-AP; $n$ = 4; Fig. 3). Injection of a large $I_{Na}$-shaped depolarizing current (10–90% rise time = 0.4 ms, $\tau_{off} = 0.6$ ms, 4-nA peak) into the dendrites during the somatic action potential reestablished the large-amplitude dendritic action potential ($69 \pm 7$ mV, $n = 4$) and the burst firing mode (ADP control: $14 \pm 1$ ms, +4-AP: $50 \pm 12$ ms, +4-AP and TTX: $24 \pm 5$ ms, +4-AP and TTX + I: $44 \pm 10$ ms, $n = 4$; Fig. 3D). Subsequent application of CdCl or NiCl (500–750 mM) blocked the ability of dendritic current injections to restore action potential bursts (ADP: $25 \pm 6$ ms, $n = 4$; Fig. 3). This indicates that the artificially produced large-amplitude dendritic spikes evoke bursting through the activation of voltage-gated Ca$^{2+}$ channels. These data support the idea that low concentrations of TTX block bursting in CA1 pyramidal neurons by inhibiting the back-propagation of action potentials into the dendritic arbor thereby reducing the prolonged Ca$^{2+}$ influx associated with dendritic spikes.

Large ADPs also could be generated even in the presence of high concentrations of TTX (300–500 $\mu$M) as long as $I_{Na}$-shaped depolarizing currents (10–90% rise time = 0.4 ms, $\tau_{off} = 0.6$ ms, 10- to 15-nA peak) were injected into the apical dendrites (Fig. 4). The amplitude and duration of these ADPs
FIG. 2. Large-amplitude dendritic action potentials activate dendritic Ca\(^{2+}\) channels. A: simultaneous somatic (top) and dendritic (bottom) recordings of membrane potential in a CA1 pyramidal cell under control conditions (no 4-AP) and with distal application of 4-AP (+4-AP). These traces demonstrate the ability of distal 4-AP application to significantly increase the amplitude and duration of the backpropagating dendritic action potential while not affecting somatic action potential parameters. B: simultaneous somatic and dendritic recordings of membrane potential in the same cell as in A now with nonspecific concentrations of NiCl (0.75 mM) in bath. - - -, control recordings shown in A for comparison. C: grouped data of action potential amplitude (left) and duration (right) for dendritic (■) and somatic recordings (□ under control (cntrl), in the presence of distal 4-AP (+4-AP) and with both 4-AP and 0.75 mM NiCl (↑[Ni]).

FIG. 3. Dendritic action potential amplitude is reduced by low concentrations of TTX. A: simultaneous recordings of somatic (top) and dendritic (bottom) membrane potential during control conditions (control) and during application of 4-AP. B: somatic and dendritic membrane potential showing the reduction in dendritic action potential amplitude induced by bath application of TTX (10 nM; traces labeled 4-AP and TTX). C: traces showing the ability of high NiCl concentrations (0.75 mM) to inhibit the burst firing recovered by dendritic current injection (traces labeled 4-AP and TTX + dend I inject and NiCl). - - -, recordings with dendritic current injection that were shown in B. D: grouped data of ADP duration under control conditions (C; □), during 4-AP application (A; ■), 4-AP and TTX application (T; ●), 4-AP and TTX application with dendritic current injection (I; ○), and 4-AP and TTX application with dendritic current injection plus 0.75 mM NiCl (N; ◆; n = 4 for all groups). E: difference trace (--; in C minus — in D) showing the effect of Ca\(^{2+}\) channel blockade on dendritic voltage. All recordings shown are from the same neuron.
could be increased by increasing the amount of current injected. In fact, a presumably Ca\(^{2+}\)-mediated spike could be initiated during the ADP if sufficiently large-amplitude currents were used (Fig. 4A; trace labeled larger I to both). The ADP again was seen to be sensitive to high concentrations of NiCl (Fig. 4, A and B). These data demonstrate that the depolarizing component involved in generating action potential bursts (the ADP) is produced primarily by current flowing through dendritic Ca\(^{2+}\) channels. Dendritic Na\(^{+}\) channels, on the other hand, provide the inward current that is needed to depolarize the membrane potential enough to activate the more prolonged dendritic Ca\(^{2+}\) current. All of this channel activation is governed by the dendritic K\(^{+}\) channels, which are able to maintain CA1 pyramidal neurons in a single-spiking mode by counterbalancing the dendritic Na\(^{+}\) and Ca\(^{2+}\) currents. Any reduction in the amplitude of this countering current is capable of moving CA1 neurons into the burst firing mode.

**Ca\(^{2+}\) channel subtypes involved in bursting**

Which specific subtypes of Ca\(^{2+}\) channels are involved in the generation of the ADP? The more distal apical dendritic arborizations of CA1 pyramidal neurons have been shown to contain a relatively high density of Ni\(^{2+}\)-sensitive (IC\(_{50} \sim 50 \mu M\)) voltage-gated Ca\(^{2+}\) channels along with a lower densities of dihydropyridine-sensitive and \(\omega\)-conotoxin MVIIIC-sensitive Ca\(^{2+}\) channels (Avery and Johnston 1996; Christie et al. 1995; Kavalali et al. 1998; Magee and Johnston 1995; Magee et al. 1996). To determine the relative contributions of the various Ca\(^{2+}\) channel subtypes to action potential bursting, we observed the ability of various channel blockers (included in either the bathing external solution or along with 4-AP in the perfusion solution) to inhibit the ADP and action potential burst firing (Fig. 5).

L-type Ca\(^{2+}\) channels are blocked by dihydropyridines and application of 10 \(\mu M\) nimodipine (a supramaximal concentration) reduced the ADP duration (45 ± 6 vs. 29 ± 3 ms, \(n = 10\), \(P = 0.04\)) and substantially reduced the number of action potential induced (5.8 ± 0.9 vs. 2.0 ± 1.0 action potentials, \(n = 10\), \(P < 0.01\)). T- and R-type Ca\(^{2+}\) channels are inhibited by low concentrations of NiCl, and application of 75 \(\mu M\) Ni\(^{2+}\) (~70% block) reduced the ADP duration (47 ± 6 vs. 25 ± 6 ms, \(n = 7\), \(P < 0.01\)) and action potential firing (6.2 ± 1.7 vs. 1.5 ± 1.0 action potentials, \(n = 7\), \(P < 0.01\)) to an even greater extent than nimodipine (\(P < 0.01\)). The combined application of NiCl and nimodipine appeared to have an additive inhibitory effect on bursting (39 ± 2 vs. 16 ± 4 ms ADP, 6.0 ± 1.0 vs. 1.0 ± 1.0 action potentials, \(n = 4\)). The N- and P/Q-type Ca\(^{2+}\) channel blocker, \(\omega\)-conotoxin MVIIIC- (1 \(\mu M\), a supramaximal concentration) had only a slight and statistically insignificant effect on action potential bursting (ADP: 39 ± 4 vs. 34 ± 5 ms; action potentials: 3.5 ± 1.7 vs. 3.2 ± 1.4, \(n = 5\)). Together these results suggest that the Ni\(^{2+}\)-sensitive Ca\(^{2+}\) channels (T and R type) play the most substantial role in the generation of somatic ADPs and action potential burst firing with L channels being next in importance and N and P/Q types playing a lessor role. This fits well with the proposed distribution of voltage-gated Ca\(^{2+}\) channels in the dendritic arbor of CA1 pyramidal neurons and further suggests that Ca\(^{2+}\) channels located within the dendrites provide the largest contribution of inward current during the ADP.

**Discussion**

In summary, it appears that dendritic K\(^{+}\) channels (primarily transient A type) regulate the action potential firing mode of CA1 pyramidal neurons by modulating the backpropagation of dendritic action potentials. Reduction of distal dendritic K\(^{+}\) current allows large-amplitude dendritic action potentials to
proficiently activate dendritic Ca\(^{2+}\) channels (primarily T and R type) substantially increasing the duration of dendritic action potentials. The Ca\(^{2+}\) current generated by these dendritic spikes propagates to the soma to produce a slow, prolonged membrane depolarization (ADP) that is capable of initiating multiple somatic/axonal action potentials. The action potential firing or output mode of the entire CA1 pyramidal neuron therefore can be regulated through an intricate interplay among the major voltage-gated ion channels (K\(^{+}\), Na\(^{+}\), and Ca\(^{2+}\)) located within the distal dendrites. With the transient A-type K\(^{+}\) channel population fully intact, the activation of dendritic Na\(^{+}\) and Ca\(^{2+}\) channels is minimal and the neuron fires single spikes. When, on the other hand, the activatable K\(^{+}\) channel population is reduced, the dendrites are allowed to provide both rapidly activating and relatively prolonged inward currents (through the activation of both Na\(^{+}\) and Ca\(^{2+}\) channels) that induce the cell to fire bursts of action potentials.

Although the importance of the transient Na\(^{+}\) current to burst firing was obvious, we found little evidence of a contribution by a persistent Na\(^{+}\) current. Indeed the enhanced sensitivity of burst firing to low TTX concentrations appeared to be associated with the low safety factor of action potential backpropagation and not to the reduction of a persistent Na\(^{+}\) current. The observation that full-amplitude ADPs could be generated in the absence of a substantial Na\(^{+}\) channel population further supports the idea that the primary role of these channels in burst firing is to allow the backpropagation of action potentials into the dendritic arbor.

The Ca\(^{2+}\) dependence of burst firing observed here was not seen in at least one previous study (Azouz et al. 1996) but has been observed in others (Andreasen and Lambert 1995; Traube et al. 1993; White et al. 1989). Although there are many methodological differences between these studies (sharp vs. patch electrodes, recording temperature, [K\(^{+}\)]\(_{o}\) species), the most straightforward explanation of the different results is that there are multiple mechanisms of burst generation in CA1 pyramidal neurons. The burst firing induced by dendritic K\(^{+}\) channel modulation may involve different mechanisms than those involved in the burst firing studied in other reports.

What physiologically relevant mechanisms exist to lower the density of dendritic K\(^{+}\) currents? Numerous neuromodulatory substances (norepinephrine, dopamine, arachidonic acid, and metabotropic glutamate) and events related with ongoing synaptic activity (membrane depolarization and elevated [K\(^{+}\)]\(_{o}\)) have all been shown to reduce the amplitude of the A-type K\(^{+}\) channels that are located in CA1 pyramidal neurons (Anderson et al. 1997; Baldwin et al. 1991; Blair et al. 1991; Chen and Wong 1991; Hoffman and Johnston 1998, 1999; Hoffman et al. 1997; Keros and McBain 1997; Villaroel and Schwarz 1996). Thus the presence of neuromodulators along with specific forms of synaptic input (highly synchronized, high-frequency, distal synaptic input) are likely to result in the generation of action potential bursts. On the other hand, lower frequency, less synchronized input will induce single action potentials. As such, both activity-dependent and methodological differences between these studies (sharp vs. patch electrodes, recording temperature, [K\(^{+}\)]\(_{o}\)) species) may influence the dependence of burst firing observed here was not seen in at least one previous study (Azouz et al. 1996) but has been observed in others (Andreasen and Lambert 1995; Traube et al. 1993; White et al. 1989). Although there are many methodological differences between these studies (sharp vs. patch electrodes, recording temperature, [K\(^{+}\)]\(_{o}\)) species), the most straightforward explanation of the different results is that there are multiple mechanisms of burst generation in CA1 pyramidal neurons. The burst firing induced by dendritic K\(^{+}\) channel modulation may involve different mechanisms than those involved in the burst firing studied in other reports.

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Burst firing has been shown to increase the probability of long-term potentiation (LTP) induction in CA1 pyramidal neurons, suggesting that information storage may be enhanced during this mode of action potential firing (Thomas et al. 1998). Along these lines, memory consolidation is hypothesized to occur primarily during the sharp wave episodes oc-
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Curren during slow wave sleep (Buzsaki 1989). Thus by modulating the action potential firing mode of CA1 pyramidal neurons dendritic voltage-gated channels may be able to fundamentally regulate hippocampal function.

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