Long-Term Potentiation in Rat Hippocampal Neurons Is Accompanied by Spatially Widespread Changes in Intrinsic Oscillatory Dynamics and Excitability

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SUMMARY

Oscillations in neural activity are a prominent feature of many brain states. Individual hippocampal neurons exhibit intrinsic membrane potential oscillations and intrinsic resonance in the theta frequency range. We found that the subthreshold resonance frequency of CA1 pyramidal neurons was location dependent, varying more than 3-fold between the soma and the distal dendrites. Furthermore, activity- and NMDA-receptor-dependent long-term plasticity increased this resonance frequency through changes in $h$ channel properties. The increase in resonance frequency and an associated reduction in excitability were nearly identical in the soma and the first 300 $\mu$m of the apical dendrites. These spatially widespread changes accompanying long-term synaptic potentiation also reduced the neuron’s ability to elicit spikes evoked through a nonpotentiated synaptic pathway. Our results suggest that the frequency response of these neurons depends on the dendritic location of their inputs and that activity can regulate their response dynamics within an oscillating neural network.

INTRODUCTION

Membrane potential oscillations (MPOs) in neurons are thought to be involved in memory encoding and network synchronization (Alonso and Garcia-Austt, 1987; Bland and Colom, 1993; Buzsaki, 2002; Engel et al., 2001; O’Keefe and Burgess, 2005). Among the roles ascribed to MPOs are augmentation of synaptic inputs that are in synchrony with MPOs (Volgushev et al., 1998), frequency selectivity (Hutcheon and Yarom, 2000; Strohmann et al., 1994), precision of action potential timing (Schaefer et al., 2006), and genesis of network rhythms (Alonso and Garcia-Austt, 1987; Buzsaki, 2002). Although oscillations in nervous systems have been studied for these and various other physiological roles they play (Buzsaki, 2002; Engel et al., 2001; Marder and Calabrese, 1996; Oestreicher et al., 2006; Ramirez et al., 2004; Steriade and Timofeev, 2003), plasticity in intrinsic subthreshold oscillatory dynamics has not been explored.

Intrinsic MPOs are mediated by voltage-gated ion channels (Hutcheon and Yarom, 2000; Linhas, 1988) and are dependent on two classes of ion-channel conductances (Hutcheon et al., 1996; Hutcheon and Yarom, 2000): (1) a resonating conductance, which forms the substrate for oscillations, determines the frequency of oscillations, governs the frequency-dependent response of the neuron, and sustains resonance on its own; and (2) an amplifying conductance, which governs the amplitude of oscillations. NMDA-type glutamate receptors and persistent sodium (NaP) channels have been suggested to act as amplifying conductances, while the $M$-type K$^+$ and hyperpolarization-activated h conductances act as resonating conductances (Hu et al., 2002; Hutcheon and Yarom, 2000). As a direct consequence of the presence of a resonating conductance, neurons endowed with intrinsic oscillations exhibit resonance, which has been used as a tool to assess their intrinsic oscillatory dynamics (Hu et al., 2002; Hutcheon et al., 1996; Hutcheon and Yarom, 2000; Leung and Yu, 1998).

In the hippocampus, MPOs during the waking state are in the theta frequency range of 3–10 Hz (Buzsaki, 2002; O’Keefe and Burgess, 2005). While theta oscillations in hippocampus are due to network interactions among pyramidal and interneurons, it is also clear that individual neurons are capable of sustaining intrinsic oscillations and that the intrinsic properties of these neurons play a prominent role in the network behavior (Buzsaki, 2002; Leung and Yim, 1991; O’Keefe and Burgess, 2005). Hippocampal CA1 pyramidal neurons exhibit subthreshold membrane potential oscillations (Leung and Yu, 1998; Leung and Yim, 1991). These neurons are endowed with the two resonating currents, $I_h$ and $I_m$, mediating resonance at hyperpolarized and depolarized voltages, respectively, with $I_h$ acting as a putative amplifying current (Hu et al., 2002; Leung and Yim, 1991).

In this study, we investigated the intrinsic subthreshold membrane resonance of CA1 pyramidal neurons and found that it was not a fixed property but instead was highly variable depending on the membrane potential, spatial location in the dendrites, and activity. The
frequency of the intrinsic resonance varied more than 3-fold between the soma and distal regions of the dendrites and was in accordance with the reported change in h-channel density (Lorincz et al., 2002; Magee, 1998). Furthermore, the induction of activity-dependent, long-term plasticity increased the resonant frequency and reduced input resistance by similar amounts in the dendrites on the apical trunk within stratum radiatum. Surprisingly, in striking contrast to the localized nature of changes in the A-type potassium current (Frick et al., 2004), we found that this plasticity is spatially widespread even when it accompanies pathway-specific long-term synaptic potentiation (LTP). Employing computational analyses, we argue that such spatially widespread changes in resonance frequency and input resistance cannot be realized through locally confined changes in \(I_h\), but require changes in h-channel properties to span a broad region of the dendritic tree. Our results suggest that these neurons can act as stimulus-dependent matched filters for spatially separated inputs, regulated by prior history of activity converging onto the neuron. Further, this spatially widespread expression of plasticity supports the role for \(I_h\) as a homeostatic mechanism counterbalancing the positive feedback associated with Hebbian plasticity (Bienenstock et al., 1982; Turrigiano and Nelson, 2000).

**RESULTS**

Resonance is the increase in the amplitude of oscillations of a system exposed to a periodic force whose frequency is equal to or very close to the natural frequency of the system. In neurons, this natural frequency corresponds to that of membrane potential oscillations (MPOs) and can be measured as the frequency at which the neuron elicits the maximal voltage response to sinusoidal current injections of various frequencies. Alternately, a sinusoidal current stimulus of constant amplitude, with frequency linearly spanning a given range over time, can be used as a tool to measure resonance properties of a neuron. Such a sinusoid has been termed a ZAP stimulus, which stands as an acronym for impedance amplitude profile (see Figure S1 available online) (Hutcheon and Yarom, 2000). In this study, we use the ZAP stimulus to characterize and assess plasticity in intrinsic membrane resonance of soma and dendrites in CA1 pyramidal neurons.

**Resonance Frequency in Dendrites Increases with Distance from Soma**

Subthreshold resonance depends on h channels (Hu et al., 2002), and h-channel density in apical dendrites increases with distance from the soma (Lorincz et al., 2002; Magee, 1998). Therefore, we tested whether this translates to location-dependence of resonance properties in the dendrites. We obtained responses of the soma and the dendrites to the ZAP20 current stimulus (Figure S1A). Our results, binned into six different distances and measured at five different subthreshold voltages, show that, irrespective of distance from the soma, resonance frequency, \(f_R\) (in the voltage range −75 mV to −55 mV), increased monotonically with hyperpolarization (Figure 1B; e.g., Soma: 1.78 ± 0.21 Hz at −55 mV to 4.92 ± 0.44 Hz at −75 mV; 300 \(\mu\)M: 3.63 ± 1.28 Hz at −55 mV to 11.10 ± 0.1 Hz at −75 mV). However, \(f_R\) in the dendrites increased considerably with increasing distance from the soma (Figure 1C). \(f_R\) at −65 mV varied from about 3 Hz in the soma to 9 Hz in a dendrite 300 \(\mu\)M from the soma. A single exponential was used to fit the experimental \(f_R\) versus distance curves with a \(\tau\) of about 75 \(\mu\)M, although sigmoidal functions could also be used (Figure S2A), especially because, at rest, dendritic \(f_R\) does not change much up to around 250 \(\mu\)M from the soma, while displaying a steep increase beyond that (Figures S2A and S2B). Resonance strength (Q) also increased with hyperpolarization (Figure 1D) and with distance from the soma (Figure 1E). Consistent with previous studies (Magee, 1998), input resistance (\(R_{in}\)) decreased with hyperpolarization (Figure 1F) and with distance from soma (Figure 1G).

**Subthreshold Resonance Is Dependent on h Channels**

Although the density of h channels (Lorincz et al., 2002; Magee, 1998) and resonance properties increase with distance from the soma, we tested directly whether \(f_R\), in fact, depended on \(I_h\). We pretreated slices for 5 min with 100 \(\mu\)M ZD7288 and assessed resonance properties (Figure S3) at various locations along the somato-apical trunk (Figure 2A), without adding ZD7288 to the recording solutions. We found that \(f_R\), along the entire measured range of voltages and distances, was below 1 Hz (Figures 2B and 2C), suggesting that blocking \(I_h\) abolished resonance in the subthreshold voltage range. This was corroborated by measurements of Q, all of which were just above the theoretical minimum of unity across the measured voltage range (Figure 2D) and distance (Figure 2E). There was a reduction in \(R_{in}\) with hyperpolarization (Figure 2F), although it remained almost constant as a function of distance (Figure 2G). Pretreatment with 20 \(\mu\)M ZD7288 led to identical results with respect to all parameters (data not shown).

Resonance observed at more depolarized voltages has been reported to be mediated by \(I_N^\text{M}\) (Hu et al., 2002). We thus tested the effects of carbachol on membrane resonance and found that it blocked resonance at depolarized potentials but had little effect on resonance at hyperpolarized potentials (Figure S4), consistent with CA1 neurons exhibiting two forms of resonance (Hu et al., 2002).

**Activity-Dependent Plasticity of Resonance Properties**

It has recently been demonstrated in CA1 pyramidal neurons that theta-burst firing (TBF) results in a reduction of excitability through increases in \(I_h\) (Fan et al., 2005). Based on the results shown above, we postulated that an activity-dependent increase in \(I_h\) should also lead to increases in both \(f_R\) and Q. To test this directly, we induced activity-dependent plasticity in \(I_h\) using the TBF protocol (Fan et al., 2005).
et al., 2005) and measured resonance properties through the course of the experiment (Figure 3).

Typical somatic responses to the ZAP15 stimulus (Figure S5B) before and 40 min after TBF illustrate an increase in \( f_R \) (Figures 3B and 3C). When the experiment was repeated over a number of cells, there was a significant increase in \( f_R \) (Figure 3D) accompanied by a significant reduction in \( R_{in} \) (Figure S5). Consistent with earlier observations (Fan et al., 2005), there was also a significant 3.25 mV depolarizing shift in resting membrane potential (RMP, \( p < 0.001 \)).

**NMDA Receptors Mediated the Resonance Plasticity**

Because previous results demonstrate that the TBF-induced plasticity in excitability is dependent on the activation of NMDA receptors (Fan et al., 2005), we tested whether the plasticity in resonance properties was also dependent on these receptors. We found that bath application of the NMDAR antagonists suppressed all TBF-induced changes, which were depolarization of the RMP, increases in \( f_R \) (Figures 3E and 3H), percentage sag, and \( Q \) (Figure 3I), and reductions in \( R_{in} \) (Figure 3F) and firing frequency (Figure S5). Changes in \( f_R \) and \( R_{in} \) were strongly correlated (Figure 3G), suggesting a common mechanism underlying changes in both the parameters; in contrast, changes during the experiments with NMDAR antagonists hovered around their respective baselines (Figure 3G).

**Plasticity in Excitability and Resonance Extends to Dendrites**

Although TBF induced plasticity in excitability and resonance as measured at the soma (Figure 3), it is not known whether this extends to plasticity in dendrites. A direct way to address this is to measure changes in excitability and resonance across the dendritic tree, using plasticity induced through TBF of axo-somatically initiated action potentials driven by antidromic stimulation (Frick et al., 2004). We refer to this form of theta-burst firing through
antidromic stimulation as antidromic TBF, or ATBF (Figure S6).

Following ATBF, there was a significant depolarizing shift in the RMP of ~3 mV at all locations measured. The time courses of reduction in $R_{in}$ (Figure 4B) and increase in $f_R$ (Figure 4C) were nearly identical at all three locations along the somato-apical trunk. The changes in $f_R$ and $R_{in}$ were strongly correlated for all three locations (Figure 4D), again suggesting a possible common mechanism underlying changes in both the parameters across the dendritic tree. Further, the percentage of changes in all measured parameters were nearly identical for all locations in the dendrites (Figure 4E). Finally, the reduction in $R_{in}$ also translated into a reduction in firing frequency of action potentials elicited in response to a range of local current injections and was observed in all three locations (Figures 4F–4I). Together, these suggest that activity-dependent plasticity in excitability and resonance were nearly identical across the somato-apical trunk.

**LTP Is Accompanied by Spatially Widespread Changes in Excitability and Resonance**

Because there have been reports of localized changes in certain ion channels accompanying LTP (Frick et al., 2004; Kim et al., 2007), we asked whether plasticity evoked by theta-burst firing pattern would remain spatially widespread (Figure 4) if this pattern is paired with orthodromic stimulation to induce LTP. A direct way to address this is to measure changes in excitability and resonance across the dendritic tree, using plasticity induced through pairing of antidromic stimulation with orthodromic stimulation (Frick et al., 2004). We refer to this form of theta-burst pairing (TBP) involving antidromic stimulation as antidromic TBP, or ATBP (Figure S7).

ATBP led to robust LTP as measured across the somato-apical trunk (Figure 5B). Further, all the changes that were observed with ATBF (Figure 4) were also obtained with ATBP (Figure 5). Specifically, across the somato-apical trunk, an ~3 mV shift in RMP, a near-identical reduction in $R_{in}$ (Figure 5C), a near-identical increase in $f_R$ (Figure 5D), correlated time courses of $R_{in}$ and $f_R$ (Figure 5E), increases in Q and sag (Figure 5F), and a reduction in action potential firing frequency (Figures 5G–5I) were observed with ATBP as well. Thus, LTP-associated plasticity in resonance and excitability were spatially widespread.

**LTP Is Accompanied by Nonlocal Reduction in Temporal Summation**

We next performed experiments to test whether temporal summation, a physiological measurement modulated by $I_h$ (Magee, 1998), also undergoes nonlocal plasticity with
LTP. First, we found that temporal summation was reduced across the dendritic tree by recording a-EPSP summation at various locations along the somato-apical trunk before and after ATBP (Figures 6A–6C). Second, we performed two-pathway LTP experiments (Figures 6D–6F) and showed that, while LTP was pathway specific (Frick et al., 2004), temporal summation of evoked EPSPs on the non-LTP pathway reduced after TBP (Figures 6G and 6H). We also showed that the number of spikes evoked through temporal summation was reduced after TBP (Figures 6I and 6J), confirming with a-EPSP summation that these changes in evoked summation were due to changes in postsynaptic components (Figures 6G–6J). Thus, even though LTP induced through TBP was local and input specific, the associated reduction in temporal summation and evoked action potentials was not local.
Resonance Properties Are Directly Related to $I_h$

Although the results described above strongly support a role for $I_h$ in subthreshold resonance, the data did not address whether there is a direct, graded relationship between $h$ conductance and resonance properties. To assess this, we constructed a simple, single-compartment model with $I_h$ as the only active current (Figure S11). When the maximal density of $h$ conductance, $g_h$, was set to zero, the response of the model (Figure 7A; $g_h = 0 \mu S/cm^2$) to the ZAP20 stimulus (Figure S1A) resembled that obtained experimentally with ZD7288 (Figure 2 and Figure S3A). The corresponding impedance amplitude
profile (Figure 7B; $g_h = 0 \, \mu\text{S/cm}^2$), with its peak around zero frequency, also was similar to the one obtained with ZD7288 (Figure S3B). This is to be expected, because without $I_h$, the model acts as a passive, parallel resistor-capacitor circuit.

When $g_h$ was increased (Figure 7A), the impedance amplitude peak shifted toward nonzero frequency values (Figure 7B), confirming that $I_h$ is a resonating conductance (Hu et al., 2002; Hutcheon et al., 1996; Hutcheon and Yarom, 2000). Importantly, we found that both $f_R$ and $Q$ increased monotonically with the increase in $g_h$, supporting the notion of a direct, graded relationship between $h$ conductance and resonance properties (Figure 7C; also see Hutcheon et al. [1996] for a rigorous mathematical analysis of a similar model).

To assess the dependence of $f_R$ and $Q$ on other parameters related to the $h$ conductance, we set $g_h$ to 60 $\mu$S/cm$^2$ so that $f_R$ was $\sim 5$ Hz at $-65$ mV. To test the effect of a shift...
in the $I_h$ activation curve on resonance properties, we plotted both $f_h$ and $Q$ as functions of $V_{1/2}$ of the $h$ conductance (Figure 7D) and found that both parameters exhibited a bell-shaped dependence on $V_{1/2}$, with their peaks occurring around the voltage at which the measurements were made ($-65$ mV). Further, simulations were in agreement with these experimental findings.
with our experimental results of an increase in both $f_h$ and $Q$ in the $-55$ mV to $-75$ mV range of membrane voltage, while also bringing out a bell-shaped curve for the $f_h$ versus $V_m$ relationship with a peak around the $V_{1/2}$ of the $h$ activation curve (Figure 7E; default $V_{1/2} = -82$ mV).

These simulations, along with the results obtained with ZD7288 (Figure 2), argue that the distance-dependent increases in $f_h$ (Figure 1) are due to an increase in $I_h$ and not due to an increase in a leak conductance. The arguments follow from the observations that there was no gradient of $R_{in}$ (or $f_R$) after blocking $I_h$ (Figures 2C and 2G); $R_{in}$ and $f_R$ were functions of membrane potential in accordance with the voltage dependence of $I_h$ (Figures 1 and 7 and Figures S1C and S3B), and $Q$ increased with distance (Figure 1E), which is a theoretical prediction for the role of $I_h$ and opposite to what would occur from an increase in leak conductance (Figure S11D). Finally, the increase in $Q$ with TBF/TBP (Figures 3–6), accompanied by a reduction in impedance amplitude at lower but not at higher frequencies (Figures 3C and 7B; Figure S7G), suggests that an increase in $I_h$ is responsible for the activity-dependent increase in $f_h$ (also see Figure S11), which conforms to earlier findings on increase in $I_h$ with TBF/TBP (Fan et al., 2005).

**Gradient in Resonance Frequency Matches Measured Gradient in h-Channel Density**

Although there is an increase in both the density of $h$ channels (Lorincz et al., 2002; Magee, 1998) and $f_h$ with distance (Figure 1C), a block of resonance by ZD7288 (Figure 2), and a direct relationship between resonance and $I_h$ (Figure 7), we do not know whether a gradient in channel density (Lorincz et al., 2002; Magee, 1998) can account for the experimentally measured gradient in resonance properties (Figure 1C). To address this question, we built a multicompartmental model with a morphologically realistic three-dimensional reconstruction of a CA1 pyramidal neuron (Figure 8A). The only active conductance we added to the model was the $h$ conductance. In deciding on the density gradient of $h$ conductance across the dendritic tree, we took into account the following experimental observations: (1) a 55- to 70-fold increase in channel density in distal dendrites with respect to that at the soma; and (2) a 13- to 25-fold increase in channel density in distal dendrites when compared to that at proximal dendrites (Lorincz et al., 2002). Quantitatively assessing the effect of various density gradients on $f_h$ (Figure S12) and taking into account these experimental measurements, we found that a $g_h$ profile that matched...
the experimental measurements of $f_R$ occurred when we used a sigmoid (80-fold increase from the soma to the distal-most point on the apical trunk; Figure 8B):

$$g_h = 34 \left( 1 + \frac{100}{1 + \exp \left( \frac{-3R}{d_R} \right)} \right) \mu S/cm^2,$$

where $d_R$ is the radial distance (in microns) of the dendritic location from the soma. Along the somato-apical trunk, $V_{1/2}$ was $-82$ mV for $d_R \leq 100$ μm, linearly varied from $-82$ mV to $-90$ mV for $100 \leq d_R \leq 300$ μm, and $-90$ mV for $d_R > 300$ μm (Magee, 1998). The basal dendrites had somatic $g_h$ and $V_{1/2}$, and apical obliques had the same $g_h$ and $V_{1/2}$, and apical obliques had the same...
Neuron Regulates Resonance Frequency Map

As the trunk compartment from which they originated (Poirazi et al., 2003). We found that \( f_h \) values obtained from simulations performed with this profile matched the experimental values of \( f_h \) quite well (Figure 8C; for \( f_h \) versus distance plots, in the 0–300 \( \mu m \) range, exponential fit [cf. Figure 1C]: \( \tau = 83.3 \mu m, \chi^2 = 3.16 \); sigmoidal fit [cf. Figure S2A]: \( x_{1/2} = 239.39 \mu m; \chi^2 = 32.78 \mu m; \chi^2 = 0.735 \)). We also could approximately match the input resistance profile (Figure 8C) and the Q profile (Figure S13A). We conclude that experimentally observed gradient in density of \( h \) channels could be theoretically accounted for experimentally observed gradient in resonance properties.

### Global Plasticity in \( I_h \) Is Required for Global Plasticity in Excitability and Excitability

From our ATBF and ATBP experiments (Figures 4 and 5), we found that plasticity in resonance properties and excitability express across a broad region of the apical dendritic tree. However, we do not know whether these changes are a result of local or global changes in \( I_h \). To address this question, we employed our multicompartimental model with \( I_h \) distributed as in Figure 8B. We considered three possible configurations for the expression of plasticity in \( I_h \): (1) plasticity confined to the soma (Figure 8D, LS); (2) plasticity confined to a local dendritic segment (Figure 8D, LD; equal amount of plasticity in 200–300 \( \mu m \) range of the apical trunk); and (3) plasticity expressed across the entire dendritic tree (Figure 8D, GL).

To effectuate an increase in \( I_h \), we either increased \( g_h \) or shifted the activation curve in the depolarizing direction, given that graded increase in \( f_h \) can be obtained by either of these manipulations (Figure 7). Under each of these two cases (increasing \( g_h \) and depolarizing \( V_{1/2} \)), we assessed the effects of increasing \( I_h \) (on \( f_h \) and \( R_{sh} \) as specified by the three possible configurations listed above (LS, LD, and GL). Our results indicated that, irrespective of whether \( I_h \) is increased through an increase in \( g_h \) or through a depolarizing shift of the activation curve, a global increase in \( I_h \) is required to bring about a global increase in resonance properties (Figures 8F and 8I and Figure S13) or a global decrease in \( R_{sh} \) (Figures 8G and 8J). More specifically, the locus of plasticity in both input resistance and \( f_h \) reflect the locus of plasticity in \( I_h \). If plasticity in \( I_h \) is confined either to the soma or to a local dendritic segment, changes in both these parameters are confined to regions adjacent to the region of expression of \( I_h \) plasticity (Figure 8 and Figure S14). Thus, we conclude that plasticity in \( I_h \) has to express across a broad region of the dendritic tree in order to achieve the spatially widespread changes observed in resonance properties and input resistance in our experiments (Figures 4 and 5).

### DISCUSSION

The primary conclusion of this study is that the intrinsic oscillatory dynamics of a pyramidal neuron are variable and plastic as a consequence of the spatial heterogeneity and plasticity of a voltage-gated ion channel. Specifically, we found that the intrinsic resonance frequency of CA1 neurons varied more than 3-fold as a function of dendritic location, due to the spatial gradient in density of \( h \) channels. Furthermore, the resonance frequency could be modified by activity-dependent long-term plasticity, which expressed over a broad region of the soma-apical trunk. This increase in resonance frequency, along with an associated reduction in excitability, remained spatially widespread even when they were accompanied by input-specific LTP. Finally, employing computational analyses, we also argued that such spatially widespread changes in resonance frequency and input resistance required changes in \( h \)-channel properties to span a broad region of the dendritic tree.

Previous studies of plasticity in oscillatory properties of neurons have focused largely on action potential firing patterns of neurons in pacemaker nuclei in electric fish (Oestreich et al., 2006), pre-Botzinger complex (Ramirez et al., 2004), and cultured vertebrate (Guertin and Hounsgaard, 2006) and invertebrate (Haedo and Golowasch, 2006; Harris-Warrick and Marder, 1991; Turrigiano et al., 1994) neurons. Change in intrinsic subthreshold oscillatory dynamics as a function of plasticity in voltage-gated ion channels has surprisingly remained unexplored, despite the numerous roles that these oscillations play in single neuron and network behavior (Alonso and Garcia-Austt, 1987; Buzsaki, 2002; Cuffles and Yarom, 2000; Linus, 1988; Schaefer et al., 2006; Strohmann et al., 1994). Expanding on our results on variability and plasticity in intrinsic resonance, we outline some important implications of these to information processing in the hippocampus.

### The Pyramidal Neuron as a Stimulus-Dependent Matched Filter

The impedance amplitude profile is a direct measure of the neuron’s response to inputs of various frequencies (Hutchon and Yarom, 2000; Strohmann et al., 1994). A CA1 pyramidal neuron (Figure S1C) functions as a band-pass filter that is optimally tuned to respond to frequencies centered on its resonance frequency. We have demonstrated that this center frequency varies as a function of spatial location in the dendrites (Figure 1C and Figure S2B). Our results suggest that proximal regions of CA1 pyramidal neurons that receive inputs from area CA3 are tuned to a lower band of frequencies (2–6 Hz), compared to distal regions that receive inputs from the entorhinal cortex (5–10 Hz). Under such a configuration, signals from these two pathways, driven by their differential points of contact on the dendritic arbor, are filtered differently before integration occurs at the soma. Such a design is reminiscent of a matched filter that is designed to match the spectral signature of the corresponding input to maximize the signal-to-noise ratio (Turin, 1960). If a CA1 pyramidal neuron implemented such a design, it would suggest that the inputs from the entorhinal cortex should...
belong to a higher frequency band than those arriving from the CA3 region. While we do not have direct evidence for this possibility (even though the existence of two independent theta sources is known [Buzsáki, 2002]), this localized filtering capability reflecting the spectral signature of various impinging inputs onto a single neuron constitutes a novel contribution of dendritic ion channels to signal integration. Neurons endowed with active dendritic trees can optimally tune their responses to multiple input sources by locally adjusting their active properties ($I_h$, in this case).

There have been previous studies, prominently in the auditory and the visual systems, where single neurons have been shown to implement such matched filters for maximizing signal-to-noise ratio (Mortensen and Nachtigall, 2000; Ricci et al., 2005). Most of these studies have focused on different neurons tuned either to different frequencies or to different aspects of the visual stimuli. In contrast, our suggestion pertains to different regions within a single neuron tuned to different frequency bands, with local dendritic ion channel properties playing a role in maximizing signal-to-noise ratio across different inputs to the neuron. Further, there have also been theoretical studies linking homeostasis (see below) and matched filters, which suggest that neurons adapting according to a stabilized Hebb rule evolve into a matched filter for the inputs that the neuron receives (Mortensen and Nachtigall, 2000).

There have also been previous studies about another resonance phenomenon associated with filtering along a dendritic cable (transfer impedance) in cortical pyramidal neurons (Ulrich, 2002). Although resonance with respect to the transfer impedance can offer insights into intraneuronal filtering and the role of ion channels in the transfer of information within the neuron (Ulrich, 2002), it would not provide a measure of how the neuron responds locally to external inputs (input impedance) arriving at various dendritic locations. Our study demonstrates that the resonance frequency associated with this input impedance is location dependent, thus revealing the possibility of a single neuron as a localized, stimulus-dependent matched filter mediated by the density of an ion channel.

**Stimulus-Adaptive Plasticity in Frequency Response**

A CA1 pyramidal neuron responds to increased activity in two ways: (1) a reduction in input resistance (Figure 3); and (2) an increase in its optimal response frequency (Figure 3C). The former may be considered as a homeostatic mechanism and is discussed in detail below. We postulate that the latter constitutes a previously unknown ability of a neuron to adapt its frequency response to optimally match the frequency of its inputs. In other words, we suggest that a CA1 pyramidal neuron can act as an adaptive matched filter, capable of tuning its frequency response to optimally and adaptively match the characteristics of inputs it receives. Such adaptability of neuronal responses to statistics of converging network activity has been argued to provide optimality in neural coding (Fairhall et al., 2001; Stemmler and Koch, 1999).

Though the timescale and the level of analysis are different, such adaptation of the system’s responses to the environment has been well characterized, especially in the visual system (HirsCh and Spinelli, 1970; Wiesel and Hubel, 1963). Further, it has also been suggested that the visual system tunes its responses to the spatiotemporal statistics of natural signals, and any alteration to these statistics also leads to an adaptation in the system response (Simoncelli and Olshausen, 2001). The mechanism proposed here can act as a substrate toward achieving similar adaptability in terms of a single neuron’s response with respect to network activity statistics.

This ability of the neuron also suggests that a single neuron’s frequency response properties could be a measure of recent activity of the network it resides in. Further, as in the CA1 pyramidal neuron, subthreshold frequency response seems to be largely guided by the $h$ conductance, this possibility also suggests that the magnitude of the $I_h$ current could act as a measure of recent network activity, with a direct relationship between activity levels and $I_h$ magnitude. This suggestion is consistent with findings that increased network activity, using high potassium external solution, increases the levels of HCN1 protein (Fan et al., 2005).

$I_h$ as a Plasticity Regulation Mechanism

Hebbian synaptic plasticity acts as a positive feedback mechanism and can destabilize a neuronal network unless concomitant homeostatic processes that can counterbalance this are activated (Turrigiano and Nelson, 2000). It has been argued that such homeostatic processes, to be effective, have to act globally and affect all synapses even if the associated synaptic plasticity is local (Bienenstock et al., 1982; Turrigiano and Nelson, 2000). This requirement on global expression of homeostatic plasticity is particularly true for CA1 pyramidal neurons for two further reasons: (1) input specificity of LTP (Figure 6), which implicates the involvement of local signals (calcium, for instance) in determining and driving plasticity confined to only certain synapses (Bliss and Collingridge, 1993), rules out a local mechanism to control plasticity across all synapses in the dendritic tree; and (2) the extracellular properties of the CA1 pyramidal neuron, which suggest that any local change of conductances does not electrically affect the entire tree (Figure 8).

It has recently been demonstrated that LTP is accompanied by an upregulation of $I_h$ (Fan et al., 2005) and LTD is accompanied by a downregulation of $I_h$ (Brager and Johnston, 2007). Combining computational methods along with these experimental results, we have argued that $I_h$ can act as a potential homeostatic mechanism for regulating plasticity by modulating intracellular calcium entry, indirectly through changes in dendritic excitability (Narayanan et al., 2005, Soc. Neurosci., abstract, 737.5). The spatially widespread expression of plasticity in $I_h$, associated with LTP leading to nonlocal changes in temporal summation (Figure 5, 6, and 8) adds more evidence to this
were performed with 10 mM MgCl₂ in a similar solution, but contained 2.5 mM KCl and 2 mM MgCl₂.

The whole-cell recording pipette solution contained (in mM) 120 K-gluconate, 10 K-2-mercaptoethanol, 20 KCl, 10 HEPES, 2 NaCl, 4 MgATP, 0.3 tris-GTP, 7 tris-phosphocreatine (pH 7.3). Neurons were visualized with differential interference contrast microscopy using a Zeiss Axioskop microscope, fitted with an Apo 63X water-immersion objective. Whole-cell patch recordings were carried out with 10 mM (+)bicuculline, 10 mM picrotoxin, 50 mM D,L-APV, and 2 mM CGP55841 added to the standard solution. While TBF experiments involved an establishment of a 5 min stable baseline of firing frequency (both measured from the ZAP15 stimulus), following an initial measurement of V-I (voltage versus current plot to measure Rm and f-I (action potential frequency as a function of depolarizing current injections) curves. Responses to the ZAP15 stimulus were measured, twice every minute, for 40 min after induction of plasticity, followed by a final measurement of the V-I and f-I curves. In addition to these, evoked EPSPs were measured at 5–7 MΩ for dendritic recordings. During the course of the experiments, an estimate of the neuron’s input resistance (denoted by Rᵢₓ) was measured from the steady-state response of the cell to a 100 pA hyperpolarizing current pulse, which also was used to monitor and compensate, if necessary, for changes in series resistance. Access resistance was 10–25 MΩ for somatic recordings and 20–40 MΩ for dendritic recordings through the period of the experiment. Data acquisition and analysis were performed with custom-written software in the Igor Pro environment (Wavemetrics).

**Measurements**

Input resistance (Rᵢₓ) was measured as the slope of a linear fit to the steady-state V-I plot obtained by injecting subthreshold current pulses of amplitudes spanning –50 pA to 50 pA, in steps of 10 pA (note that this is different from Rᵢₓ in Figures 1 and 2). Action potential firing frequency was computed by extrapolating the number of spikes obtained during a 700 ms current injection to 1 s. Stimulus used for characterizing the impedance amplitude profile (ZAP) was a sinusoidal current of constant amplitude, with its frequency linearly spanning 0–20 Hz in 20 s (ZAP20; Figure S1A). The ZAP stimulus used for plasticity experiments (Figures 3–6) had its frequency linearly span 0–15 Hz in 5 s (ZAP15; Figure S5B). The reason behind using a shorter version of the ZAP stimulus was to obtain two responses to the stimulus per minute, with enough interspersal interval to compensate for series resistance changes, if necessary. The magnitude of the ratio of the Fourier transform of the voltage response to the Fourier transform of the ZAP stimulus formed the impedance amplitude profile. The frequency at which the impedance amplitude reached its maximum was the resonance frequency (fₒ). Resonance strength (Q) was measured as the ratio of the maximum impedance amplitude to the impedance amplitude at 0.5 Hz (Hu et al., 2002). Percentage sag was measured from the voltage response of the cell to a hyperpolarizing current pulse of 100 pA and was defined as 100 × (1 – Vₒ/Vₒₓ), where Vₒ was the steady-state voltage deflection from baseline, and Vₒₓ was the peak voltage deflection from baseline. EPSP slope was computed as the slope of the linear fit to the first 2 ms rising period of an EPSP. a-EPSPs were evoked by current injections of the form Iₓ = Iₓ max × exp (−x/t), with x = 0.1. Temporal summation ratio in a train of EPSPs was computed as Eₓ/2/Eₓ, where Eₓ and Eₓ/2 were the amplitudes of last and first EPSPs in the train, respectively. Voltages have not been corrected for the theoretical liquid junction potential, which was calculated to be ~14 mV based on relative ionic mobilities and charge.

**Plasticity Protocols**

The experimental protocol for TBF (Figure 3) and ATBF (Figure 4) experiments involved an establishment of a 5 min stable baseline of Iₓ and Rᵢₓ (both measured from the ZAP15 stimulus), following an initial measurement of V-I (voltage versus current plot to measure Rᵢₓ and f-I (action potential frequency as a function of depolarizing current injections) curves. Responses to the ZAP15 stimulus were measured, twice every minute, for 40 min after induction of plasticity, followed by a final measurement of the V-I and f-I curves. In addition to these, evoked EPSPs were measured at 5–5 mV peak and were monitored after plasticity induction with measurements made twice every minute. In two-pathway TBF experiments (Figure 6), evoked EPSPs from both pathways were measured twice every minute, with the measurement of the two EPSPs separated by ~16 s (on either side of the ZAP15 stimulus). Details of plasticity induction for each of these cases are provided in respective figure legends. For all plasticity experiments, recordings were carried out at the initial resting membrane potential through the course of the experiment.

**Data Analysis**

In characterization experiments (Figures 1 and 2), values at each “holding voltage” were averages of measurements obtained by injecting the ZAP20 stimulus five times. In plasticity experiments (Figures 3–6),
baseline values of EPSP slope, \( f_p \), sag, and \( Q \) were obtained by averaging measurements over the entire 5 min baseline period, and postplasticity values were obtained by averaging measurements from the 35–40 min period after induction of plasticity. For time course plots (e.g., Figure 3E), two successive measurements were averaged to obtain a single data value for each minute, and this value was divided by the average baseline value throughout to obtain the normalized time course. Group data are expressed as mean ± SEM. Depending on the dataset, statistical significance was calculated using paired or unpaired Student’s t tests, Mann-Whitney, ANOVA, or the Kruskal-Wallis tests. Post hoc tests following significance with the Dunn’s test. Correlation was assessed using the Pearson’s correlation test.

Computer Simulations

Simulations were performed using the NEURON simulation environment (Carnevale and Hines, 2006). Integration time step for all simulations was set at 25 μs. Temperature was set at 34°C. The single-compartment model (Figure S11A) was a cylinder of 100 μm length and 100 μm diameter. \( R_m \) was set as 30 kΩ·cm², and \( C_m \) was 1 μF/cm². ZAP20 current stimulus (Figure S1A) was injected to obtain measurements of \( f_p \) and \( R_p \) under various parametric variations. The kinetics of the only active mechanism in the model, the \( h \) channel, were set in accordance with experimental measurements (Figure S11B) from the CA1 pyramidal neuron (Magee, 1998). Cell 4123 (Figure 8A) from the Duke-Southampton archive (http://neuron.duke.edu/cells/) was used for all multicompartmental simulations. Passive properties were set as in Poirazi et al. (2003). All multicompartmental simulations were performed at –65 mV.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/56/6/1061/DC1/.

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