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Minireview

The Back and Forth of Dendritic Plasticity

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Synapses are located throughout the often-elaborate dendritic tree of central neurons. Hebbian models of plasticity require temporal association between synaptic input and neuronal output to produce long-term potentiation of excitatory transmission. Recent studies have highlighted how active dendritic spiking mechanisms control this association. Here, we review new work showing that associative synaptic plasticity can be generated without neuronal output and that the interplay between neuronal architecture and the active electrical properties of the dendritic tree regulates synaptic plasticity.

The dendritic tree is the input area of a neuron, receiving thousands of synapses. Dendrites have long been considered to simply funnel synaptic potentials from their site of generation to the soma and axon, where they are integrated to initiate action potential firing. However, electrophysiological recording, imaging and computer simulation have shown that dendrites are far more than passive cables: they not only shape, compartmentalize, and integrate synaptic inputs, but also transmit regenerative signals (Hausser et al., 2000). Here, we review, with reference to recent work published in *Neuron*, the role that dendrites play in the control of synaptic plasticity.

How Do the Active and Passive Properties of Dendrites Control the Induction of Synaptic Plasticity?

A key active process is action potential backpropagation (Magee and Johnston, 1997; Markram et al., 1997; Stuart and Sakmann, 1994; Yuste and Denk, 1995). The backpropagating action potential (BPAP) may be considered as a retrograde signal that broadcasts the occurrence of neuronal output throughout the dendritic tree. Hebb's learning rule requires that a synaptic input must help to drive neuronal output for the input to be potentiated. BPAPs provide a natural substrate for this time-dependent association of input and output at activated synapses. In many classes of neuron, the repeated pairing of synaptic input with neuronal output induces robust synaptic plasticity, with the sign dictated by the interval and order of EPSP and action potential generation (Dan and Poo, 2004). Typically, long-term potentiation (LTP) is evoked when synaptic input precedes, and so contributes to, action potential output and long-term depression (LTD) when synaptic input follows action potential output (Dan and Poo, 2004). The induction of EPSP-action potential pairing LTP requires active action potential backpropagation and, in common with other forms of LTP, the synaptic activation of NMDA-type glutamate receptors, which cooperatively provide the calcium influx necessary to spark the induction of plasticity (Magee and Johnston, 1997). Imaging has shown that a supra-linear calcium influx in dendritic spines occurs at activated synapses when a BPAP rides on the peak or decaying phase of an EPSP (Koester and Sakmann, 1998); focusing the primary mechanism of LTP induction on the voltage-dependent properties of NMDA receptors, where magnesium block of the channel pore is relieved by membrane depolarization to allow fractional calcium entry (Figure 1). In support of this, recent voltage-imaging studies have demonstrated that BPAPs strongly invade dendritic spines (Nuriya et al., 2006) and so can control the membrane potential at single excitatory synapses.

This compelling mechanism has several drawbacks, principle among which is the nonuniformity of action potential backpropagation (Lisman and Spruston, 2005). BPAPs decrementally invade the dendritic tree, often failing at sites distal from the soma (Hausser et al., 2000; Spruston et al., 1995), and so penetrate into some but not all dendritic branches because of constraints imposed by dendritic morphology and the nonuniform distribution of voltage-activated ion channels (Rall, 1977; Vetter et al., 2001). The rules for the induction of spike-timing-dependent plasticity (STDP) may therefore be distinct for synapses positioned at dendritic sites close to or far from the soma (Dan and Poo, 2004). For example, in hippocampal CA1 pyramidal neurons, robust EPSP-action potential pairing LTP can be evoked at proximal apical, but not distal apical dendritic synapses (Golding et al., 2002), a finding that correlates well with the decremental invasion of BPAPs (Spruston et al., 1995). Furthermore, in neocortical layer 5 pyramidal neurons, STDP rules are distinct for excitatory inputs targeted to proximal and distal dendritic sites, with the same EPSP to action potential timing producing LTP at proximal synapses, but LTD at distal synapses (Sjostrom and Hausser, 2006). In layer 5 pyramidal neurons the amplitude of BPAPs declines with distance into the apical dendritic arbor but may be boosted by the provision of additional dendritic depolarization (Stuart and Hausser, 2001; Williams and Stuart, 2000a). Sjostrom and Hausser (2006) elegantly demonstrated that procedures that boost BPAP amplitude also rescue the induction of LTP at distal apical dendritic sites. Thus, the amplitude and time course of BPAPs at

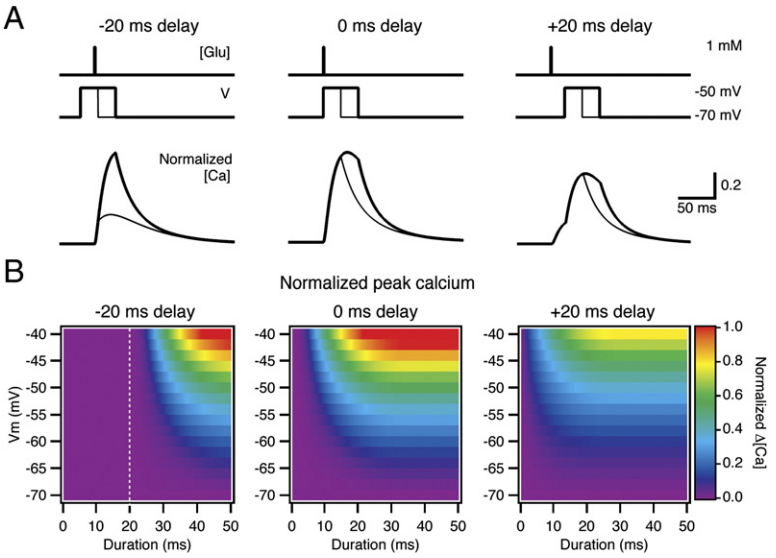

Figure 1. Voltage- and Time-Dependent Gating of Calcium Influx through the NMDA Receptor

(A) The duration of depolarization dictates calcium entry in a biophysically realistic NMDA receptor model (Kampa et al., 2004). The NMDA receptor was activated by 1 ms pulse of glutamate (1 mM) and voltage stepped from −70 to −50 mV for 25 (thin traces) or 50 ms (thick traces), with a delay of −20, 0, or 20 ms relative to the onset of the glutamate pulse. When paired at −20 ms, the duration of the depolarization critically determines the calcium concentration ([Ca]), estimated from the calcium current (E_{Ca} = 50 mV) convolved with a 20 ms single exponential function (Sabatini et al., 2002). Peak [Ca] was normalized to that at −70 mV.

(B) Surface plots showing peak [Ca] as a function of the amplitude and duration of membrane potential steps, for delays of −20, 0, or 20 ms relative to glutamate pulse onset. Dashed line in the left plot indicates the timing of the glutamate pulse. Peak [Ca] was normalized to that at −70 mV.

the dendritic site of EPSP generation may be a determining factor for the induction of STDP. As NMDA receptors function as a voltage-dependent calcium source, the time-course and amplitude of the BPAP voltage waveform will determine the degree of calcium entry generated during the pairing of EPSPs and action potentials (Kampa et al., 2004; Letzkus et al., 2006) and thus the sign and magnitude of plasticity (Figure 1).

Are BPAPs a Unique Associative Signal for the Induction of Timing-Dependent Plasticity?

Recently, it has become clear that action potential firing is unnecessary for the induction of some forms of synaptic plasticity. For example, the induction of synaptic plasticity at excitatory synapses located distally in the apical dendritic tree of CA1 pyramidal neurons does not require BPAPs as an associative signal but instead requires the generation of local dendritic spikes (Golding et al., 2002). In CA1 and classes of neocortical pyramidal neurons dendritic synaptic integration can result in the generation of dendritic spikes. Dendritic spikes are greatest in amplitude at site of generation and can either be confined locally to individual dendritic branches (Losonczy and Magee, 2006), regions of the dendritic arbor (Schiller et al., 1997), or actively propagate through the dendritic tree to the soma and axon (Williams, 2004). Although dendritic spikes do not represent neuronal output, they are a product of postsynaptic integration and so can be considered as the output of a dendritic compartment. As the induction of action potential-independent LTP at distal apical dendritic sites of CA1 pyramidal neurons requires the activation of NMDA receptors and voltage-dependent calcium channels, it is clear that regenerative events such as dendritic spikes can act as a cooperative signal for the induction of plasticity (Golding et al., 2002). Factors that control the activation of dendritic calcium channels may therefore influence the induction of synaptic plasticity.

A class of voltage-activated channels termed *h*yperpolarization-activated *c*yclic *n*ucleotide gated (HCN) channels, profoundly shapes the function of the apical dendritic arbor of CA1 and large neocortical pyramidal neurons (Magee, 1999; Stuart and Spruston, 1998; Williams and Stuart, 2000b). HCN1 channels are expressed at high density in the apical dendritic tree (Lorincz et al., 2002) and control the attenuation of synaptic potentials as they spread through the dendritic arbor and set the time-window for their integration (Magee, 2000). Importantly, genetic deletion has shown that HCN1 channels control the induction of cooperative LTP at distal apical dendritic sites of mouse CA1 pyramidal neurons, a cellular phenotype paralleled by altered spatial learning behavior (Nolan et al., 2004).

In this issue of *Neuron*, Tsay et al. (2007) demonstrate that HCN channels constrain dendritic calcium electrogenesis, providing a mechanistic link with the control of cooperative synaptic plasticity. Tsay et al. (2007) use two-photon calcium imaging of the terminal apical dendrites of mouse CA1 pyramidal neurons to explore how HCN channels control calcium signals evoked by high frequency burst activation of excitatory glutamatergic synapses of the perforant path, a pattern of activity that can induce cooperative synaptic plasticity. In common with previous findings, they show that calcium responses are mediated by the regenerative activation of dendritic calcium channels, triggered by synaptic excitation, that leads to slow, often subthreshold, somatic voltage responses (Golding et al., 2002; Wei et al., 2001). Importantly, Tsay et al. (2007) show that the duration and amplitude of distal dendritic calcium signals were enhanced by the pharmacological block of HCN channels, an effect paralleled by changes in the somatic voltage waveform. Similarly, the amplitude and time-course of dendritic calcium and somatic voltage signals were increased in HCN1 knockout mice. Interestingly, Tsay et al. (2007) argue that HCN

channels do not constrain dendritic electrogenesis simply by acting as a shunt conductance or because of their voltage-dependent activation/deactivation properties, but also by controlling the membrane potential at distal apical dendritic sites.

I_H, the macroscopic current mediated by HCN channels, is a noninactivating current with a reversal potential of around −30 mV (Pape, 1996). About 10% of HCN channels are open at, and help to maintain, the resting membrane potential of many classes of neurons (Pape, 1996). Previous findings have indicated that the calcium channels underlying distal dendritic electrogenesis in CA1 pyramidal neurons are inactivated by membrane depolarization (Cai et al., 2004; Wei et al., 2001). Therefore, the control of membrane potential by I_H may act to keep a fraction of dendritic calcium channels inactivated, which can become available for activation following membrane hyperpolarization elicited by the block of HCN channels and so increase dendritic calcium signaling (Tsay et al., 2007). To experimentally test this idea, Tsay et al. (2007) show that offsetting the membrane potential hyperpolarization produced by blockade of HCN channels with depolarization generated by raising extracellular potassium levels prevented changes in the amplitude and duration of distal dendritic electrogenesis. Although crude, these data are supportive of the notion that HCN channels influence calcium entry, at least in part, by modulating the voltage-dependent availability of calcium channels. This mechanism is reminiscent of the role that HCN channels play in thalamocortical and Purkinje neurons, where control of membrane potential sets the availability of low-threshold calcium and persistent sodium channels, respectively (Pape, 1996; Williams et al., 2002). As a number of neurotransmitter systems modulate the activation properties of HCN channels (Magee, 2000; Pape, 1996), and so membrane potential, the neuromodulation of HCN channels may dynamically control calcium signaling in the apical dendritic arbor of CA1 pyramidal neurons. HCN channels should not, however, be considered sole gatekeepers of dendritic electrogenesis. The amplitude and time course of dendritic spikes are powerfully constrained by voltage- and calcium-activated potassium channels (Cai et al., 2004; Golding et al., 1999). Dendritic potassium and perhaps calcium channels are also subject to neuromodulation (Magee and Johnston, 2005). Many classes of voltage-activated ion channels therefore control dendritic calcium electrogenesis, the orchestrated modulation of which may be required to provide a permissive signal for the induction of cooperative synaptic plasticity.

Does the Associative Signal for Synaptic Plasticity Have to Be a BPAP or Dendritic Spike?

In a recent issue of *Neuron*, Dudman et al. (2007) show that associative, timing-dependent LTP can be induced entirely in the subthreshold domain. In the new work on hippocampal CA1 pyramidal neurons, excitatory synaptic input is *not* paired with action potential output, but rather with the activation of a separate excitatory pathway, emulating the natural temporal sequence of activity in the hippocampal circuit (Dudman et al., 2007). CA1 pyramidal neurons receive two streams of excitatory input originating from the entorhinal cortex. A direct pathway, the perforant path (PP), synapses at distal apical dendritic sites in the stratum lacunosum-moleculare (SLM), whereas an indirect trisynaptic pathway, formed by the sequential activation of dentate granule cells and CA3 pyramdial neurons, innervates CA1 pyramids at proximal apical dendritic sites in the stratum radiatum (SR) as Schaffer collateral (SC) synapses (Figure 2). This circuitry introduces a time delay between the arrival of streams of excitatory input to CA1 pyramidal neurons, as synaptic and integrative delays ensure that the indirect pathway is time-lagged by 10 to 20 ms (Yeckel and Berger, 1990). Dudman and colleagues simply asked if emulation of this natural time delay would allow timing-dependent plasticity when a subthreshold EPSP generated by electrical stimulation of the PP path was repeatedly paired with a subthreshold EPSP generated by electrical stimulation of SC 20 ms later. Surprisingly, during whole-cell current-clamp recording of mouse CA1 pyramidal neurons in vitro, the presentation of 90 paired PP and SC EPSPs at low frequency led to a dramatic and long lasting, input-specific, potentiation of the SC EPSP (Figure 2). Such input-timing-dependent plasticity (ITDP) was induced only when EPSPs were paired within a narrow time window centered on a disparity of 20 ms and was specific for the sequence of PP before SC activation. This form of LTP was both NMDA and metabotropic glutamate receptor dependent and required calcium release from intracellular stores (Figure 2). Although evoked EPSPs in each pathway were of large amplitude and so represent the near synchronous activation of a number of synapses, EPSPs were *subthreshold* for the generation of action potentials when applied alone or when paired. Moreover, in a separate group of experiments, whole-cell recordings from the trunk of the apical dendrite and calcium imaging indicated that single or paired SC and PP EPSPs did not evoke dendritic spikes (Dudman et al., 2007). This is an important issue, as the generation of a single dendritic spike can lead to long-lasting potentiation of SC EPSPs (Remy and Spruston, 2007).

If spikes are not involved, how does this subthreshold temporal association induce synaptic plasticity? Calcium imaging showed that the association of subthreshold EPSPs leads to a dramatic timing-dependent increase in intraspine calcium (Dudman et al., 2007). The PP EPSP might therefore operate as a surrogate spike, acting in the same way as a burst of BPAPs does in other neurons, when associated at times preceding EPSPs, by providing depolarization that overlaps in time the synaptic activation of NMDA receptors (Letzkus et al., 2006). Surprisingly, however, ITDP and enhanced spine calcium were not observed when two, presumably independent, SC inputs were paired at 20 ms or closer intervals. What then is special about the perforant path EPSP? Two key features arise simply because of dendritic architecture; first, EPSPs are electrically filtered as they spread from site of

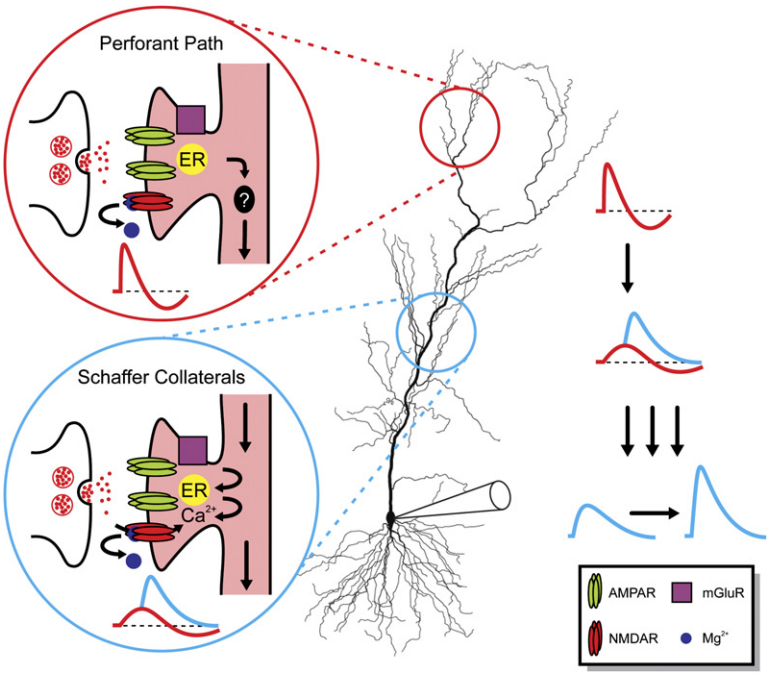

Figure 2. Schematic Representation of Dendritic Integration during Input-Timing-Dependent Plasticity in a CA1 Pyramidal Neuron

Potentiation of the amplitude of Schaffer collateral EPSPs (blue lower traces) is evoked when a perforant path EPSP (red) and Schaffer collateral EPSP are paired at a critical time interval (overlaid red and blue traces). The calcium sources that underlie the induction of this form of long-term potentiation are cartooned within a Schaffer collateral spine (blue circle). It is proposed that potentiation results from calcium entry through NMDA receptors and calcium release from intracellular stores following the activation of metabotropic glutamate receptors. The possible requirement for an intersynaptic signaling molecule is indicated by the filled black circle.

generation through the dendritic arbor (Magee, 2000; Rall, 1977; Williams and Stuart, 2002). In a passive system, filtering will decrease the amplitude but increase the duration of a PP EPSP as it spreads to the stratum radiatum, providing an ideal platform for temporal summation with SC EPSPs (Figure 3). Second, the architecture of the neuron protects the SC synapse from the conductance change associated with the PP input, as synaptic conductance is "visible" across the dendritic arbor over a shorter distance than voltage (Williams, 2004). Consistent with this, Dudman et al. (2007) show that a slow PP and SC EPSP effectively summate, while two SC EPSPs do not, presumably because of the localized shunting effects of neighboring SC inputs. The summed PP + SC spine head EPSP may be of sufficient amplitude to open voltage-activated channels (Araya et al., 2007; Sabatini and Svoboda, 2000) that act to amplify calcium entry, a process that may not be detectable electrically from the apical dendritic truck or soma. An alternative possibility that Dudman et al. concentrate on is the role played by the

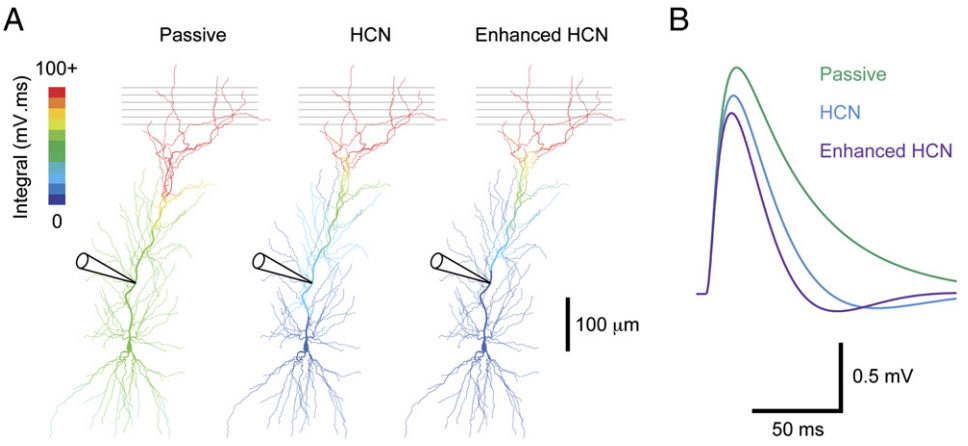

Figure 3. HCN Channels Compartmentalize Distal Dendritic Excitation in CA1 Pyramidal Neurons

(A) Compartmentalization of distal dendritic excitation in a biophysically realistic CA1 pyramidal neuron model (Golding et al., 2005). The synchronous activation of 40 excitatory perforant path synapses generates large voltage responses within the stratum lacunosum-moleculare (red). EPSPs attenuate as they spread through the dendritic arbor to the soma (colder colors). In a passive dendritic tree EPSPs propagate effectively (left). The spread of EPSPs is however, increasingly constrained as the density of HCN channels is increased from physiological (middle) to enhanced levels (three times density, right). The perforant path is represented as horizontal lines. Each synaptic input was modeled as: $E_{synapse}$ = 0 mV; $g_{synapse}$ = 0.1 nS; τ_{rise} = 0.5 ms; τ_{decay} = 5 ms.

(B) The amplitude and time course of EPSPs recorded from a dendritic site within the stratum radiatum (145 μm from soma) is constrained by HCN channels.

slow summed PP + SC EPSP in relieving the time- and voltage-dependent magnesium block of the NMDA receptor. Using a biophysically realistic NMDA receptor model, simulation demonstrated that this may be an important mechanism, where the slow PP + SC EPSP provides an effective signal for the unblock of NMDA channels, because the PP input provides long-lasting depolarization that overlaps in time with activation of the SC synapse (Dudman et al., 2007; Figure 1). They further test this idea by showing paired PP + SC EPSPs generate greater NMDA receptor-mediated calcium entry than *larger* amplitude, but *faster* voltage changes produced by paired SC EPSPs or SC EPSPs paired with a BPAP. It is important to note that in experiment, depolarization generated at the soma was not able to substitute for the PP EPSP. This may be because somatic depolarization failed to supply adequate voltage at the SC synapses, as its magnitude is bounded by the generation of action potentials. This data indicate, however, that depolarization from the basal dendritic arbor should not associate with apical dendritic EPSPs. To more rigorously test their hypothesis, Dudman and colleagues could have mimicked the amplitude and time course of PP EPSPs by current injection during dendritic recording experiments. Nevertheless, they convincingly show that PP and SC EPSPs can conspire to induce LTP that does not require the generation of full-blown action potentials or dendritic spikes but requires calcium entry through NMDA receptors and the release of calcium from intracellular stores. It remains to be established if interaction between PP and SC synapses is mediated purely by membrane voltage or if a biochemical signal is also required (Figure 2).

These exciting results prompt many questions. Previous findings have indicated that the concerted influences of dendritic architecture, synaptic inhibition, and the recruitment of voltage-activated channels, compartmentalizes PP excitation within the stratum lacunosum-moleculare (Ang et al., 2005; Golding et al., 2005; Nicholson et al., 2006; Nolan et al., 2004). Consequently, it is unclear how widespread the spatial influence of ITDP will be across SC synapses of the stratum radiatum (Figure 3). As the thin terminal dendrites of CA1 pyramidal neurons powerfully attenuate EPSPs as they spread to the stratum radiatum, a large number of PP synapses must be synchronously activated to achieve EPSPs of amplitude large enough to underlie ITDP (Golding et al., 2005; Nicholson et al., 2006). Although the synchronous activation of the perforant path is easily achieved by electrical stimulation, it remains to be demonstrated physiologically. Several factors will influence the time-window of ITDP induction. First, feed-forward synaptic inhibition controls the time course of SC and PP EPSPs (Ang et al., 2005; Pouille and Scanziani, 2001), and so the recruitment of inhibitory elements may be important for the manifestation of ITDP with a time relationship appropriate for the hippocampal circuit. The involvement of inhibition suggests that the use-dependent dynamics of synaptic transmission may influence the impact of PP synapses. For example, when PP and SC pathways are paired with the same delay as used by Dudman et al. (2007), but driven in a theta burst pattern, the PP input does not *cause*, but *prevents* SC LTP, because of the recruitment of overwhelming synaptic inhibition (Remondes and Schuman, 2002). Second, HCN channels control the amplitude and time course of PP EPSPs as they spread through the dendritic tree, and so will powerfully influence the voltage integral of PP EPSPs at SC synapses, the crucial trigger for ITDP (Figure 3; Golding et al., 2005; Magee, 1999; Nolan et al., 2004). A neuromodulation of the voltage-dependent activation properties (Magee, 2000; Pape, 1996), and/or an activity-dependent modulation of HCN channel density may therefore control the spatial extent, timing specificity and sustainability of ITDP and perhaps other forms of LTP (Figure 3).

LTP Reshapes Dendritic Integration

The induction of synaptic plasticity is accompanied by changes in neuronal excitability (Bliss and Gardner-Medwin, 1973; Zhang and Linden, 2003). In vitro studies have shown excitability changes are, at least in part, intrinsic to the postsynaptic neuron (Daoudal et al., 2002; Fan et al., 2005; Frick et al., 2004; Wang et al., 2003; Xu et al., 2005). Pioneering work suggested that orchestrated plasticity of synaptic and neuronal excitability might function synergistically (Bliss and Gardner-Medwin, 1973). In support of this, the induction of LTP has been shown to be accompanied by postsynaptic changes in the availability of voltage-activated channels, that at the soma reduce action potential firing threshold and in dendrites enhance action potential backpropagation and the summation of EPSPs (Daoudal et al., 2002; Fan et al., 2005; Frick et al., 2004; Wang et al., 2003; Xu et al., 2005). Enhanced excitability may, however, have deleterious effects, allowing all excitatory inputs to have a greater impact on neuronal output. This outcome can be alleviated by the modification of voltage-activated channels only in a dendritic region surrounding the site of potentiated synapses (Daoudal et al., 2002; Frick et al., 2004; Wang et al., 2003).

In this issue of *Neuron*, Narayanan and Johnston (2007) elegantly demonstrate an alternative: that the induction of LTP is accompanied by a global, rather than local, modification of the integrative properties of the dendritic tree. The new work builds on a previous study showing that the induction of LTP, or simply the delivery of theta burst action potential firing patterns unpaired with synaptic input, leads to a decrease in the somatic input resistance of CA1 pyramidal neurons, mediated by the upregulation of HCN channels (Fan et al., 2005). In common with synaptic plasticity, this form of intrinsic plasticity requires action potential backpropagation and is NMDA receptor-dependent (Fan et al., 2005). Thus, potentiation of excitatory synaptic transmission can be accompanied by a decrease in intrinsic excitability. As HCN channels are predominately distributed at apical dendritic sites in CA1 pyramidal neurons, Narayanan and Johnston (2007) asked if the induction of LTP is accompanied by the upregulation of HCN channels throughout the dendritic arbor.

To do this, they examined the frequency dependence of dendritic integration by delivering short bursts of time varying current through whole-cell recording electrodes placed at sites along the apical dendritic trunk of rat CA1 pyramidal neurons in vitro (Narayanan and Johnston, 2007). The current signal, an impedance amplitude profile (ZAP), was composed of sine waves of increasing frequency (0 to 20 Hz). In a passive system, the greatest voltage response evoked by a ZAP function is at low frequency (Hutcheon and Yarom, 2000). When voltage-activated channels are recruited, however, frequency dependence is influenced by the time and voltage-dependent availability of ion channels, and so the peak voltage response, the resonance frequency, is dictated by ion channel composition (Hutcheon and Yarom, 2000). Interestingly, Narayanan and Johnston (2007) found the resonance frequency of CA1 neurons varied across the somatoapical dendritic axis, with resonance frequency and power increasing from 3 Hz at the soma to 9 Hz at distal apical dendritic sites. Both experiment and simulation demonstrated that the kinetic properties and the predominant apical dendritic distribution of HCN channels were necessary and sufficient to explain this distance-dependent behavior. The subcellular distribution of a class of ion channel therefore sets in a site-dependent manner the frequency dependence of dendritic integration (Narayanan and Johnston, 2007). Although the physiological significance of this behavior can only be speculated, these results suggest that different areas of the dendritic arbor are tuned to frequencies that broadly span the theta band (4–10 Hz), the dominant frequency range of the hippocampus. It should be noted that these effects are highly voltage dependent, with both the power and frequency of resonance decreasing with membrane depolarization, consistent with the voltage-dependence of HCN channel activation (Pape, 1996). These data, together with others (Ulrich, 2002), provide a fresh way of quantifying the subthreshold behavior of dendrites and underscore that the integrative properties of dendrites are not uniform, but are site dependent (Magee, 1999; Williams and Stuart, 2002).

Narayanan and Johnston (2007) found that the induction of LTP modifies the frequency responsiveness of dendrites, shifting resonance to higher frequencies across the somatoapical dendritic axis. The time course of this effect paralleled that of LTP, and changes in resonance were correlated with a decrease in apparent input resistance at somatic and apical dendritic sites. Furthermore, at recording sites across the apical dendritic trunk, the amount of injected current required to generate action potential firing was increased, as was the ability of evoked or simulated trains of EPSPs to drive action potential output. As HCN channels heavily influence resonance and the somatic impact of apical dendritic excitation, Narayanan and Johnston asked if activity-dependent changes of the properties or density of HCN channels could explain such a global decrease in excitability. Simulations showed that only a widespread increase in the density or change in the activation properties of HCN channels throughout the dendritic arbor could explain the spatially widespread changes in resonance and excitability (Narayanan and Johnston, 2007). The new results therefore indicate that LTP is accompanied by intrinsic plasticity that is spatially widespread and controls the frequency dependence of dendritic integration. The physiological role played by modification of the frequency tuning of a neuron or neuronal compartment remains uncertain. It could, for example, function to match or enhance responsiveness to the frequency characteristics of the input, in order to facilitate signal detection in a noisy environment. The mechanisms underlying the upregulation of HCN channel function are also unclear. Insight from this and previous work highlight the importance of calcium-signaling mechanisms involving action potential backpropagation and NMDA receptor activation (Fan et al., 2005; Narayanan and Johnston, 2007). Consistent with an important role for BPAPs, the upregulation of somatic HCN channels is not manifest when LTP is evoked by synaptic tetanic stimuli that generate only sparse action potential firing (Fan et al., 2005). How these signals lead to the upregulation of HCN channel function is unknown, but protein translation inhibitors prevent this effect, and HCN protein levels are increased by chemically induced action potential firing (Fan et al., 2005), pointing toward an increase of HCN channel density rather than modulation of their activation properties as a likely mechanism. Conversely, recent data has shown that the induction of LTD in CA1 pyramidal neurons is accompanied by increased neuronal excitability (Brager and Johnston, 2007). This form of intrinsic plasticity, examined at the level of the soma, is mediated by the downregulation of HCN channels, triggered by the synaptic activation of metabotropic glutamate receptors (Brager and Johnston, 2007). Thus, the sign of changes in intrinsic excitability can parallel those of synaptic plasticity through the bidirectional regulation of HCN channels (Brager and Johnston, 2007; Narayanan and Johnston, 2007).

A Platform for Plasticity

The reviewed data argue that the architecture of the dendritic tree and its complement of voltage-activated channels provide a platform for the induction and dynamic control of synaptic plasticity. Key effectors are HCN channels that control the electrical geometry of the dendritic tree (Stuart and Spruston, 1998), influencing the impact that synaptic inputs have on action potential output and the propagation of regenerative activity. The widespread regulation of HCN channel density throughout the dendritic tree reported in this issue of *Neuron* may therefore represent an important regulator of synaptic plasticity. For example, dendritic membrane potential depolarization produced by the upregulation of HCN channels (Narayanan and Johnston, 2007) may act to gate cooperative LTP generated at distal apical dendritic sites (Tsay et al., 2007). Whereas increased voltage attenuation produced by upregulation of HCN channels will curtail the spread of subthreshold excitation within the dendritic arbor and so control ITDP (Dudman et al., 2007; Figure 3).

Interestingly, action potential-dependent forms of intrinsic plasticity may play a supervisory role, allowing the induction of synaptic plasticity by action potential-independent mechanisms that involve dendritic integration (Dudman et al., 2007; Golding et al., 2002; Tsay et al., 2007) to thrive until checked when a critical level of neuronal output is achieved. The dampening of dendritic excitability, together with homeostatic synaptic regulatory mechanisms (Turrigiano and Nelson, 2004) may therefore prevent the runaway saturation of excitatory synaptic transmission.

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