Plasticity of Dendritic Excitability

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ABSTRACT: Dendrites are equipped with a plethora of voltage-gated ion channels that greatly enrich the computational and storage capacity of neurons. The excitability of dendrites and dendritic function display plasticity under diverse circumstances such as neuromodulation, adaptation, learning and memory, trauma, or disorders. This adaptability arises from alterations in the biophysical properties or the expression levels of voltage-gated ion channels—induced by the activity of neurotransmitters, neuromodulators, and second-messenger cascades. In this review we discuss how this plasticity of dendritic excitability could alter information transfer and processing within dendrites, neurons, and neural networks under physiological and pathological conditions. © 2005 Wiley Periodicals, Inc. J Neurobiol 64: 100–115, 2005

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BACKGROUND

Plasticity of Neurons and Neural Networks

The term *neural plasticity* comprises not only the formation and storage of memories, but also such phenomena as neuromodulation, sensory adaptation to environmental changes, or even traumatic events and pathological conditions. Mechanisms contributing to neural plasticity include rewiring of neuronal circuits, generation of new neurons, remodeling of dendrites, synaptic plasticity, and plasticity of neuronal excitability (Martin and Morris, 2002; Zhang and Linden, 2003).

Information flow between neurons within a neural network is a complex process that involves the following (rather simplified) sequence of events: presynaptic release of neurotransmitter, transduction by the postsynaptic side, synaptic integration, action potential (AP) output, back-flow of information into the dendritic arbors, and retrograde signaling towards the presynapse. All these processes are shaped by the intrinsic excitability of the neuron. As a result, plasticity of intrinsic excitability will alter the transfer, processing, and storage of information within single neurons and their associated neural networks (for reviews, see Harris-Warrick and Marder, 1991; Marder et al., 1996; Turrigiano and Nelson, 2000; Giese et al., 2001; Daoudal and Debanne, 2003; Zhang and Linden, 2003).

A Definition of Intrinsic Plasticity. Intrinsic plasticity is defined here as a modulation of either the functional state or the expression level of ion channels in the neuronal membrane, thereby altering the membrane excitability (Hille 2001). The cellular locus of this change will largely determine the outcome for neuronal computation; for example, a change in the excitability of the AP initiation zone (close to the soma) globally modifies the efficacy of most synaptic inputs to trigger an AP. Intrinsic plasticity confined to a dendritic branch or module, on the other hand, could alter the local integration and efficacy of only a few (or even single) synaptic inputs. In addition to

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spatial considerations, time is a crucial factor determining the impact of intrinsic plasticity on neuronal function. This intrinsic plasticity could transiently and/or persistently tune the excitability of neurons and neural networks, and thus contribute to the formation of short- and long-term memory traces or the emergence of pathological syndromes such as epilepsy.

Homeostatic Regulation of Neuronal Activity. The intrinsic excitability of individual neurons plays an important role in regulating the amount of input necessary to evoke an action potential, the firing rate and pattern, and, therefore, network dynamics. Research on both invertebrate and vertebrate systems has demonstrated the existence of homeostatic changes in intrinsic excitability, which could stabilize neuronal activity levels. In these studies, sustained alterations in activity led to accompanying changes in the expression of voltage-gated ion channels that shape neuronal firing patterns (Turrigiano et al., 1994, 1995; Desai et al., 1999; Golowasch et al, 1999; Nick and Ribera, 2000; Baines et al., 2001; Aizenman et al., 2003). For example, in cultured neocortical pyramidal neurons, blocking activity for hours or days can lower the threshold of AP initiation and increase the firing frequency in response to current injections at the cell body (Desai et al., 1999). These changes result from an upregulation of Na^{+} channels and a downregulation of sustained K^{+} currents. Conversely, elevated activity levels result in a homeostatic downregulation of AP output through opposite modulations of the underlying currents. In addition, neuronal firing properties can also adapt in response to rapid changes in signaling (Aizenman and Linden, 2000; Armano et al., 2000; 0Ganguly et al., 2000; Egorov et al., 2002; Nelson et al., 2003; Sourdet et al., 2003; Li et al., 2004; Cudmore and Turrigiano, 2004; Misonou et al., 2004; van Welie et al., 2004). For example, in deep cerebellar nuclei neurons, brief high-frequency synaptic activity induces a persistent increase in intrinsic excitability within minutes of tetanization (Aizenman and Linden, 2000). As a consequence, the neurons display a lower AP threshold and an increase in the number of APs in response to somatic depolarization.

Compensatory homeostatic plasticity mechanisms, including intrinsic plasticity, scaling of synaptic strength, and changes in inhibition, ensure that a neuron can operate in its optimal range by normalizing the overall excitability, and promote network stability (Spitzer, 1999; Stemmler and Koch, 1999; Abbott and Nelson, 2000; Turrigiano and Nelson, 2000; Marder and Prinz, 2002; Piedras-Renteria et al., 2004). Without these stabilizing feedback mechanisms, Hebbian plasticity or acute changes in intrinsic plasticity could lead to a destabilization of postsynaptic firing, resulting in extremely high or low AP discharge rates.

Intrinsic Plasticity Induced by Learning Tasks

Studies on invertebrate and vertebrate organisms have implicated changes in intrinsic excitability in various learning tasks (reviewed in Giese et al., 2001; Doudal and Debanne, 2003; Zhang and Linden, 2003). Early evidence linking behavioral training with intrinsic plasticity derives from the pioneering work by Alkon and colleagues on the nudibranch mollusk, *Hermissenda* (Alkon et al., 1982; Alkon, 1984; Alkon et al., 1985). In these studies, classical conditioning of the phototaxic response induced a conditioned response, parallel with a long-lasting (weeks) increase in the excitability of the photoreceptor cell. This intrinsic plasticity was expressed as an increase in the number of APs evoked by either a light-stimulus or somatic current injection, and resulted from a second messenger-induced decrease in transient A-type K^{+} currents and Ca^{2+}-dependent K^{+} currents. Other studies that followed—associative conditioning in the terrestrial snail *Helix* (Gainutdinov et al., 1998) and in the marine mollusk *Aplysia* (Antonov et al., 2001), operant conditioning in *Aplysia* (Brembs et al., 2002), as well as sensitization in *Aplysia* (Cleary et al., 1998) and the medicinal leech *Hirudo* (Burrell et al., 2001)—were all accompanied by neuron type-specific increases in intrinsic excitability. In contrast to sensitization, habituation of the shortening response in *Hirudo* led to a decrease in intrinsic excitability of the same neuron type.

In vertebrates, learning task-related changes in intrinsic excitability have been reported in a number of brain regions. Possibly the first evidence for intrinsic plasticity induced by behavioral training came from research by Brons and Woody (1980). In their studies, associative conditioning in cats resulted in a persistent increase (enduring at least 28 days) in neuronal excitability in the pericruciate sensorimotor cortex, as revealed by intracellular recordings from conscious animals. In a different learning-task, trace eyeblink conditioning in rabbits induced a transient (< 7 days) increase in excitability in the CA1 and CA3 region of the hippocampus, as confirmed by recordings from pyramidal neurons in hippocampal slices following the training. Neurons from trained animals display an increased AP discharge in response to depolarizing current injection, and a reduced ampli-

tude of the afterhyperpolarization (AHP; Disterhoft et al., 1986; Coulter et al., 1989; de Jonge et al., 1990; Moyer et al., 1996; Thompson et al., 1996). In contrast to trace eye-blink conditioning, delay eye-blink conditioning requires the cerebellar network and leads to an enduring (> 30 days after training) increase in intrinsic excitability spatially limited to a defined microzone. Within this region, the dendrites of Purkinje cells were more excitable, showing a lower threshold for triggering spikes and a reduced AHP [Table 1 and Fig. 1(B); Schreurs et al., 1997, 1998]. Operant conditioning, on the other hand, was found to temporarily increase the excitability of layer 2 pyramidal neurons in piriform cortex for up to 5 to 7 days, and this has been suggested to enable rule learning (Saar et al., 1998, 2001; reviewed in Saar and Barkai, 2003). Additional evidence for a reduction of the AHP induced by learning is provided by a recent study of spatial learning in a watermaze task (Oh et al., 2003). Voltage-clamp recordings indicated a reduction in one or more of the currents underlying the AHP of CA1 pyramidal neurons in the dorsal but not ventral hippocampus. A recent study of Pavlovian conditioning in the amygdala further supports the idea that changes in excitability are linked to synaptic plasticity or the formation of memory (Rosenkranz and Grace, 2002). *In vivo* intracellular recordings from anesthetized rats revealed that repeated pairings of an odor with a footshock led to increases in synaptic strength and in neuronal excitability. These studies support a role for intrinsic plasticity in learning and memory, and at least some of this plasticity likely occurs in the dendrites.

Active Properties of Dendrites Are Malleable

Dendrites are elaborate structures that collect thousands of synaptic inputs and integrate them in a complicated and incompletely understood process to trigger an AP output of the neuron (Spruston et al., 1999; Reyes, 2001; Gulledge et al., p. 75, this issue). Important determinants of synaptic integration are the morphology, as well as the passive and active properties of the dendritic arbor. Dendrites owe their active properties to the presence of numerous voltage-dependent ion channels, which greatly increase the computational complexity of single neurons. Electrophysiological recordings and imaging studies have revealed the existence of voltage-gated Na^{+}, Ca^{2+}, and K^{+} channels in the dendrites and even in the dendritic spines (Magee, 1999; Reyes, 2001; Tsay and Yuste, 2004). The impact of these channels on synaptic integration depends on the amplitude, time course, and spatial location of the synaptic signals, as well as the distribution and the densities of the channels. Strongly synchronized or clustered synaptic inputs, or glutamatergic stimulation can lead to the generation of Na^{+} and/or Ca^{2+} spikes in hippocampal and neocortical dendrites (Schiller et al., 1997; Schwindt and Crill, 1997a; Golding and Spruston, 1998; Kamondi et al., 1998; Helmchen et al., 1999; Frick et al., 2001; Larkum and Zhu, 2002). In addition, in some neuron types APs initiated in the axo-somatic region actively back-propagate into the dendritic tree (Johnston et al., 1996; Yuste and Tank, 1996; Stuart et al., 1997). Both back-propagating APs (bAPs) and dendritically initiated spikes can release the Mg^{2+} block of NMDA receptors as well as evoke dendritic calcium influx through voltage-gated Ca^{2+} channels, and have been shown to be involved in the induction of synaptic plasticity at proximal and distal synapses, respectively (Magee and Johnston, 1997; Markram and Sakmann, 1997; Golding et al., 2002).

Modulation of Dendritic Voltage-Gated Channels. Most of the voltage-gated channels found in dendrites can be modulated by a variety of neurotransmitters, modulators, and second messenger systems. Modulation can affect channel properties such as the voltage-dependence of activation and inactivation, gating, and the probability of opening, as well as the expression levels of these channels in the membrane. Consequently, the intrinsic excitability of dendrites can be modified in numerous ways. Moreover, many of these signaling pathways are triggered by activity patterns that are known to occur *in vivo*. In addition, some of these activity patterns will also trigger changes in synaptic strength, raising the possibility that both synaptic and intrinsic plasticity could be induced in parallel, and act synergistically to promote the formation of memories.

Na^{+} Channels. The modulation of voltage-dependent Na^{+} channels (for review, see Cantrell and Catterall, 2001) has important consequences for dendritic and overall neuronal excitability. A broad array of neurotransmitters—monoamines, peptides, acetylcholine, glutamate—have been shown to alter Na^{+} channel function in neurons, primarily via phosphorylation (through protein kinases A and C) and dephosphorylation (e.g., calcium-regulated phosphatase calcineurin and protein phosphatase 2A) of the pore-forming α subunits.

Phosphorylation of Na^{+} channels can result in smaller Na^{+} currents (Cantrell and Catterall, 2001), or decrease their activation by shifting the voltage-dependence of activation to more depolarized poten-

Table 1 Activity-Dependent Plasticity of Dendritic Excitability

Activity	Neuron	Induction/modulation	Channel	Channel Effect	Dendritic Function
[1]Behavioral task	CA1 pyramids	NMDAR; acetylcholine?/kinases?	I_{Na}, I_A, or M?	Decrease I_A, slow I_{Na} inactivation or M?	↑ excitability, bAP train
[2]Classical conditioning	Purkinje cells, rabbit	?/?	I_A; I_{AHP}?	Decrease I_A	↑ excitability, Ca^{2+} spike initiation; ↓ hyperpolarization/AHP
[3]TBP	CA1 pyramids	NMDAR/ERK?	I_A	Left-shift inactivation curve	↑ excitability, bAPs & Ca^{2+}
[4]Correlated pre-/post synaptic activity	CA1 pyramids	NMDAR, L-type Ca^{2+} channel/ PKC & CaMKII; adenylate cyclase?	NMDAR & I_h	Bidirectional	bidirectional effect on EPSP summation
[5]Brief trains of bAPs	CA1 pyramids	Ca^{2+}, L-type Ca^{2+} channel/CaMKII	$I_{Ca,R}$	Depression	↓ spine Ca^{2+} influx; inhibition of LTP
[6]Depolarization pulses	CA1 pyramids, mouse	Ca^{2+}/CaMKII & cAMP	I_{Na}?	Decrease slow inactivation?	↑ excitability, bAP train
[7]TLE, chronic	CA1 pyramids	?/ERK	I_A	Reduction in channel density and function	↑ excitability, bAPs

[1]Quirk et al., 2001; [2]Schreurs et al., 1997, 1998; [3]Frick et al., 2004; [4]Wang et al., 2003; [5]Yasuda et al., 2003; [6]Tsubokawa et al., 2000, [7]Bernard et al., 2004.
TBP, theta-burst pairing; ERK, extracellular signal-regulated kinase; PKC, protein kinase C; CaMKII, Ca^{2+}/calmodulin-dependent kinase; TLE, temporal lobe epilepsy.

tials (Gasparini and Magee, 2002), resulting in a decrease in neuronal excitability. Other studies report either an increase (Carr et al., 2003), or a decrease (Colbert and Johnston, 1998) in the slow inactivation of Na^+ channels (Colbert et al., 1997; Jung et al., 1997), which could modulate the frequency-dependent attenuation of the bAP amplitude during a train. Finally, modulation may differentially affect transient or persistent Na^+ currents (Maurice et al., 2001).

Ca^{2+} Channels. Activation of voltage-gated Ca^{2+} channels in the dendrites provides additional inward current and further increases the excitability of the dendrites. Importantly, these channels provide a pathway for Ca^{2+} influx, thereby linking electrical activity and intracellular signaling cascades.

Ca^{2+} channels can be modulated by G proteins, phosphorylation, and, in a negative feedback loop, by Ca^{2+} itself (reviewed in Catteral, 2000). In hippocampal neurons, activation of metabotropic glutamate, $GABA_B$, somatostatin, serotonin, or adenosine receptors has been reported to inhibit dendritic Ca^{2+} channels (Chen and Lambert, 1997; Kavalali et al., 1997). The largest impact of these G-protein–mediated mechanisms is on dendritic N-type Ca^{2+} channels. In cultured mitral cells, norepinephrine (via α2-adrenoceptor activation) effectively reduced dendritic Ca^{2+} influx evoked by depolarization (Bischofberger and Schild, 1995), presumably by inhibiting N-type Ca^{2+} channels. Based on somatic studies, β-adrenoceptor activation would be expected to increase Ca^{2+} influx through certain types of dendritic Ca^{2+} channels (Fisher and Johnston, 1990; Hoogland and Saggau 2004).

K^+ Channels. Voltage-dependent K^+ channels are the primary regulators of dendritic excitability. Delayed rectifiers, M-, D-, A-type, and G protein-activated inward rectifying K^+ (GIRK) channels have all been found in the dendrites of CA1 and/or neocortical pyramidal neurons (Hoffman et al., 1997; Takigawa and Alzheimer, 1999; Bekkers, 2000; Korngreen and Sakmann, 2000; Chen and Johnston, 2004).

Phosphorylation plays a key role in modulation of K^+ channels by altering the amplitude, kinetics, or channel expression in the plasma membrane. For example, Kv4.2, the major subunit contributing to dendritic A-type K^+ currents in CA1 pyramidal neurons, has phosphorylation sites for PKA, PKC, MAPK, and CaMKII (reviewed in Schrader et al., 2002). Activation of PKA, PKC, and MAPK by neuromodulators [noradrenaline, dopamine, acetylcholine, glutamate (via mGluRs)] decreases the activity of these dendritic A-type K^+ channels (Hoffman and Johnston, 1998, 1999; Yuan et al., 2002). Activation

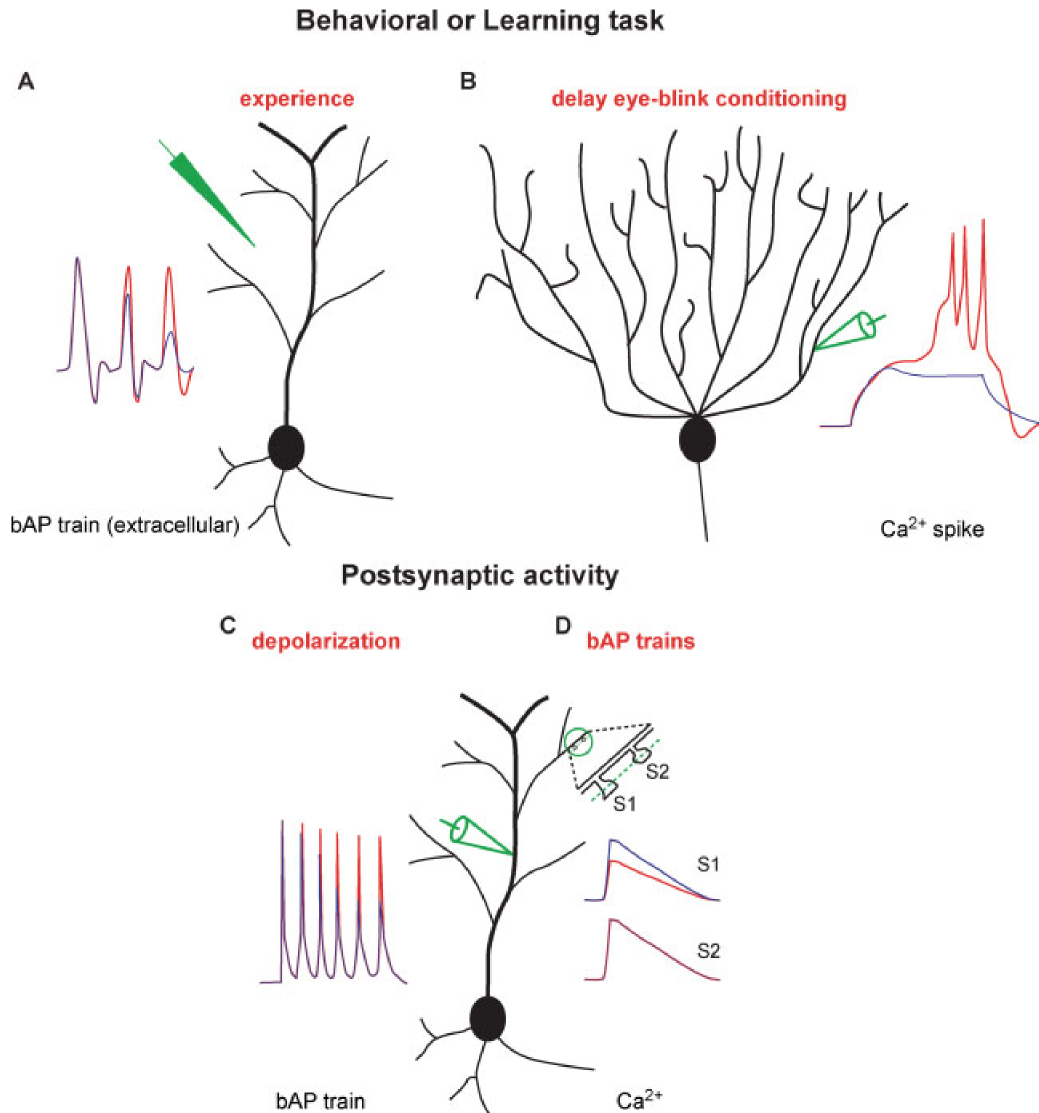

Figure 1 Dendritic intrinsic plasticity induced by behavioral tasks, learning tasks, and postsynaptic activity. (A) The frequency-dependent decline of dendritic bAP amplitude is reduced with experience. Spikes are recorded *in vivo* using extracellular electrodes in the CA1 region of the hippocampus. *Blue* trace, the amplitude of bAPs progressively declines during a train of spikes. *Red* trace, experience in an environment leads to a reduction in the degree of this attenuation, suggesting an increase in the effectiveness of back-propagation. (B) Classical conditioning increases dendritic excitability of Purkinje cells in rabbits. Dendritic recordings were made from cerebellar slices that were taken 1 month after 3 days of classical conditioning (*red* trace) or unpaired stimulus presentation (*blue* trace). The threshold to evoke local dendritic Ca^{2+} spikes in Purkinje cells is lower in slices from animals that received classical conditioning. (C) The frequency-dependent decline of dendritic bAP amplitude is reduced following depolarization and Ca^{2+} influx. Dendritic recordings were made from CA1 pyramidal neurons in mouse hippocampal slices. *Blue* trace, control. *Red* trace, after a series of depolarizing current injections (and Ca^{2+} influx) into the dendrite, the AP back-propagation is persistently improved. (D) Postsynaptic activity depresses bAP-evoked Ca^{2+} influx into individual spines in CA1 pyramidal neurons. *Blue* traces, Ca^{2+} transients evoked by a single bAP in two spines in control. *Red* traces, brief trains of APs persistently reduced this Ca^{2+} influx through R-type Ca^{2+} channels in some spines (S1) but not in the parent dendrite or neighboring spines (S2), suggesting that intrinsic plasticity can be restricted to individual spines. [The illustrations were adapted from (A) Quirk et al., 2001; (B) Schreurs et al., 1998; (C) Tsubokawa et al., 2000; and (D) Yasuda et al., 2003].

of CaMKII, on the other hand, seems to alter their surface expression (Varga et al., 2004). Phosphorylation and dephosphorylation of delayed rectifiers (Kv2.1 in neocortex and hippocampus) can affect their localization and voltage-dependent activation properties (Misonou et al., 2004). GIRK channels are activated by hyperpolarizations and their activation is increased by the neuromodulators adenosine and serotonin, and by $GABA_B$ receptor activation (Andrade et al., 1986). M-type K^+ channels can be inhibited by synaptically released acetylcholine via activation of muscarinic receptors (Gähwiler and Brown, 1985; Madison et al., 1987). Effective modulation of voltage-gated K^+ channels can also occur through membrane phospholipids and their metabolites (Ramakers and Storm, 2002; Colbert and Pan, 1999). A recent study (Oliver et al., 2004) of recombinant K^+ channels provided evidence that phosphoinositides can convert transient channels into delayed rectifiers, while arachidonic acid and anandamide conferred rapid voltage-dependent inactivation into non-inactivating channels.

H Channels. In the dendrites of several neuron types (hippocampal CA1 pyramidal neurons, neocortical pyramidal neurons, and cerebellar Purkinje cells) membrane hyperpolarizations evoke inward currents via h channels that are slowly activating and deactivating and virtually non-inactivating (Häusser and Clark, 1997; Schwindt and Crill, 1997b; Magee, 1998; Stuart and Spruston, 1998). These h channels have a strong impact on the firing properties of neurons and synaptic integration (Pape, 1996; Magee, 1999; Robinson and Siegelbaum, 2003; Shah et al., 2004).

The activation properties of I_h are very sensitive to intracellular concentrations of cAMP and cGMP (Pape, 1996). Increases in the levels of cAMP and cGMP (such as via β-adrenoceptor activation or application of nitric oxide) shift the voltage dependence for activation of I_h towards more depolarized potentials, enhancing channel activation at resting membrane potentials. Conversely, a decrease in cyclic nucleotide levels has the opposite effect.

Relative Densities of Inward and Outward Currents. Depending on the type of channel, activation of these conductances can either enhance or dampen the integration and propagation of dendritic signals. Consequently, the relative densities of inward (Na^+ and Ca^{2+}) and outward (K^+) currents located within the membrane have a profound impact on the excitability of the dendritic membrane (Magee, 1999; Reyes, 2001). This ratio can vary across the dendritic arbor due to non-uniform distributions of the channels and modulation. For instance, in hippocampal CA1 pyramidal neurons there is an increase in A-type K^+ channels with distance from the soma (Hoffman et al., 1997). Similarly, in CA1 and neocortical pyramidal neurons, the densities of I_h increase steeply with distance, strongly influencing membrane properties and synaptic integration in the distal dendrites (Magee, 1998; Williams and Stuart, 2000; Berger et al., 2001; Lorincz et al., 2002). An alternative means of altering the balance of inward and outward currents is via differences in their functional state (for recent review see Reyes, 2001). In fact, Na^+, A-type K^+, N-type Ca^{2+}, and h channels show different properties in the distal versus proximal dendrites, presumably as a consequence of gradients in second messenger-systems (Bischofsberger and Schild, 1995; Hoffman et al., 1997; Colbert and Johnston, 1998; Magee, 1998).

Modifications of dendritic channel properties or densities via neuromodulator-induced activation of intracellular cascades are potential forms of intrinsic plasticity. However, an important question is *how does plasticity of dendritic excitability contribute to the computation and storage of information in dendrites, neurons, and neural networks?*

INTRINSIC PLASTICITY OF DENDRITES

Plasticity of Action Potential Back-Propagation

As mentioned above, in many neuron types APs travel not only in a forward direction along the axon, but also back into the dendrites (Johnston et al., 1996; Yuste and Tank, 1996; Stuart et al., 1997). These dendritic bAPs have been recorded *in vitro* as well as *in vivo* (Buzsaki et al., 1996; Helmchen et al., 1999), and have been implicated in spike-timing–dependent plasticity (STDP; Magee and Johnston, 1997; Markram et al., 1997; Linden, 1999; Sourdet and Debanne, 1999; Bi and Poo; 2001, Sjöstrom and Nelson, 2002). Moreover, the coincidence of bAPs with distal synaptic input can facilitate the initiation of dendritic Ca^{2+} spikes, which in turn evoke somatic AP bursts (Larkum et al., 1999). The mode of AP back-propagation can be either fully regenerative, decremental, or passive, and depends upon the geometry (Vetter et al., 2001; Schaefer et al., 2003) and intrinsic excitability of the dendritic tree (Migliore and Shepherd, 2002). This excitability is highly state dependent and modifiable by factors such as neuromodulation, inhibitory or excitatory synaptic input, to name a few. In hippocampal and neocortical pyramidal neurons, bAP

trains are characterized by a frequency-dependent decline in the dendritic spike amplitude, progressively limiting their dendritic invasion (Andreasen and Lambert, 1995; Callaway and Ross, 1995; Spruston et al., 1995; Stuart et al., 1997). This property is voltage dependent and can be partly attributed to the slow inactivation of dendritic Na^+ channels that lasts seconds (Colbert et al., 1997; Jung et al., 1997). In contrast to single bAPs, which mostly activate rapid conductances, spike trains will activate, and consequently be shaped by both fast and slow conductances, providing additional targets for modulation. Overall, intrinsic excitability along the dendritic arbor has a strong impact on the spatial and temporal profile of AP back-propagation and its associated Ca^+ influx.

Evidence that activity can increase the effectiveness of dendritic AP back-propagation may be found in a study by Tsubokawa and colleagues [see Table 1 and Fig. 1(C); Tsubokawa et al., 2000]; strong depolarization of the dendrites of CA1 pyramidal neurons led to a persistent reduction in the attenuation of bAPs within trains. This form of activity-dependent plasticity required an increase in $[Ca^{2+}]$ in the apical dendrite, and was mediated by the activation of CaMKII. *In vivo*, the modulation of dendritic ion channels, and consequently back-propagation, may occur with behavioral experience. In a study by Quirk and coworkers using freely behaving animals, the degree of AP attenuation recorded extracellularly in rat hippocampus was reduced by an animal's experience within a particular environment [see Table 1 and Fig. 1(A); Quirk et al., 2001]. This alteration depended on the activation of NMDA receptors, suggesting the engagement of plasticity mechanisms during behavior. Due to the infancy of this field, many questions remain: for example, can this form of plasticity be triggered by activity patterns that are known to induce LTP? Is it input-specific and localized with respect to the LTP induction site? Which channels are modulated to cause this change in conductivity? We recently addressed some of these issues using dendritic recordings and Ca^{2+} imaging combined with long-term plasticity studies in CA1 pyramidal neurons [Table 1 and Fig. 2(B); Frick et al., 2004]. Dendritic branches that received bursts of synaptic input at theta frequency, properly timed with bAPs, displayed not only a long-term potentiation (LTP) of synaptic strength, but also a persistent increase of intrinsic excitability. As a result, the back-propagation of APs and the influx of their associated Ca^{2+} signals were enhanced in a spatially restricted manner. Further analysis revealed a hyperpolarized shift in the inactivation curve of A-type K^+ channels in this dendritic region, thereby reducing their availability for activation. This reduction of I_A would remove some of the restraints for AP back-propagation (Hoffman et al., 1997; Frick et al., 2003). In the distal dendrites, this increased excitability may switch the AP back-propagation from a passive to an active one (Magee and Johnston, 1997; Stuart and Häusser, 2001; Bernard and Johnston, 2003). Similarly, differences in the ratio of inward-to-outward currents in the distal dendrites of CA1 pyramidal neurons have been suggested to confer strong or weak back-propagation in separate neuron populations (Golding et al., 2001). Another, even more localized form of intrinsic plasticity has been reported by Yasuda and colleagues [2003; Table 1 and Fig. 1(D)]. In this study, short trains of bAPs depressed the bAP-evoked Ca^{2+} influx through R-type Ca^{2+} channels in individual spines, but did not affect the channels in the parent dendrites or neighboring spines. This suggests that the bAP amplitude itself was not modified, but that intrinsic plasticity can be focused to the scale of a single synapse.

Together these studies promote the idea that the back-propagation of APs is not a fixed entity, but instead is malleable by the recent activity of the neuron. Modulation of bAPs during specific activity patterns *in vitro* or during behavior *in vivo* would be expected to affect Ca^{2+} signals and STDP differently across the dendritic arbors (Magee and Johnston, 1997; Sourdet and Debanne, 1999; Mainen, 1999; Bi and Poo, 2001; Sjöström and Nelson, 2002; Watanabe et al., 2002).

Plasticity of Dendritic Integration

The active properties of dendrites play an important role in synaptic integration. In particular Na^+, A-type K^+, T-type Ca^{2+}, and h channels can all influence and/or be influenced by subthreshold EPSPs (for reviews, see Magee, 1999; Reyes, 2001). Intrinsic plasticity of the dendrites could therefore alter the Ca^{2+} influx into spines, the summation of synaptic potentials, the detection of coincident inputs, and the pairing of synaptic potentials with AP output (Häusser and Mel, 2003).

The pioneering work performed by Bliss and Gardner-Medwin (1973) taught us that tetanic stimulation in the hippocampus can induce LTP as well as increase the propensity of a neuron to fire APs in response to a given EPSP—a phenomenon termed EPSP-to-spike potentiation (E-S potentiation; for reviews, see Daoudal and Debanne, 2003; Zhang and Linden, 2003). Some subsequent studies attribute E-S potentiation to plasticity of dendritic conductances,

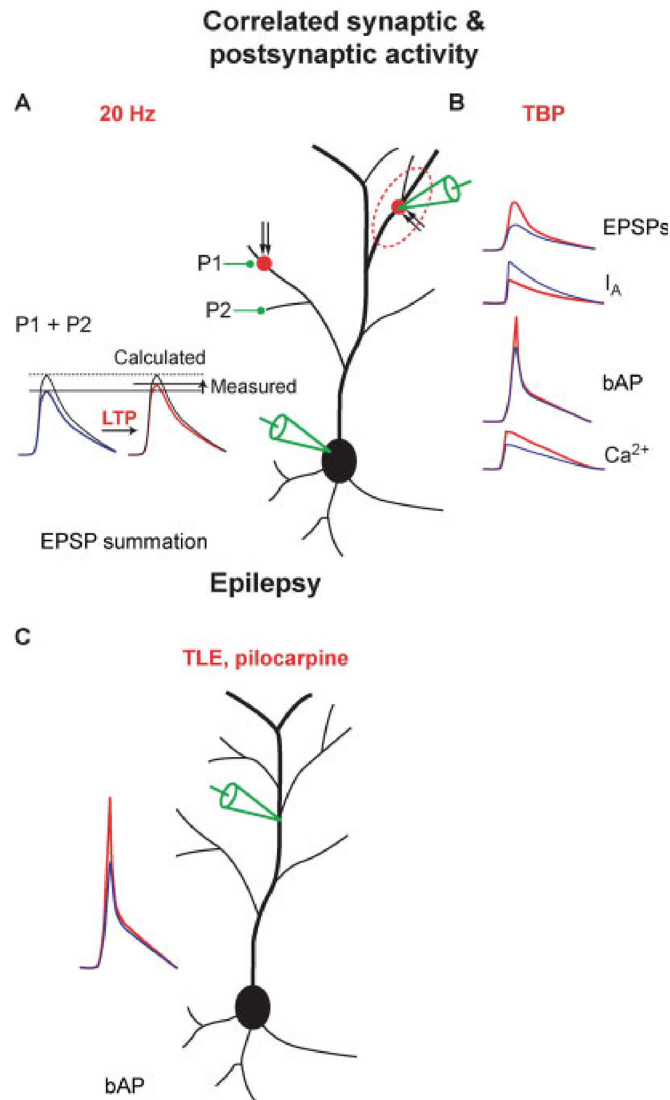

Figure 2 Dendritic intrinsic plasticity induced by correlated pre- and postsynaptic activity, and by epilepsy. (A) The induction of LTP is accompanied by improved spatial summation of EPSPs. Recordings were made from the soma of CA1 pyramidal neurons. The measured summation of EPSPs, evoked by synchronous stimulation of two different pathways (P1 and P2), resulted in sub-linear summation when compared to the calculated summation (sum of separate EPSPs). *Blue* trace, measured summation in control. *Red* trace, the spatial summation is increased following the induction of LTP at P1 (arrows), suggesting a change in active conductances. (B) The excitability of a localized dendritic module increases following the induction of LTP. Changes were measured using dendritic recordings combined with Ca^{2+} imaging in CA1 pyramidal neurons. *Blue* traces, control. *Red* traces, after LTP induction (arrows), a region of increased dendritic excitability exists surrounding the potentiated synapses. Top, LTP of synaptic strength. Second row, the activation of A-type K^+ channels is inhibited in this region. This is associated with a persistent and localized enhancement of AP back-propagation (third row), and of Ca^{2+} influx triggered by the bAP (fourth row), suggesting that intrinsic plasticity can be restricted to dendritic branches. (C) AP back-propagation is enhanced in a pilocarpine model of temporal lobe epilepsy (TLE). Recordings were made from the dendrites of CA1 pyramidal neurons in hippocampal slices. *Blue* trace, in sham animals, the bAP amplitude is small in the distal dendrites. *Red* trace, in slices taken from epileptic animals, the bAP amplitude was strongly increased, suggesting a modification of the ratio of inward to outward current in the dendrites. [The illustrations were adapted from (A) Wang et al., 2003; (B) Frick et al., 2004 and Häusser, 2004; and (C) Bernard et al., 2004].

further supporting the idea that activity patterns that induce LTP may also trigger intrinsic plasticity. For example, current-source density analyses have demonstrated a shift of current sinks into the dendrite following LTP induction, indicating an increase in the activation of voltage-dependent channels in the dendrites (Taube and Schwarzkroin, 1988a; Vida et al., 1995). This conclusion has been verified more directly using dendritic recordings (Taube and Schwarzkroin, 1988b). As mentioned previously, one important issue concerns the spatial extent of intrinsic plasticity with respect to the dendritic compartment that receives the potentiated synaptic inputs. In CA1 pyramidal neurons, correlated pre- and postsynaptic activity that induced LTP or LTD also produced persistent bidirectional changes in the spatial summation of neighboring inputs along the apical dendrite [Table 1 and Fig. 2(A); Wang et al., 2003]. The authors proposed that modifications of dendritic h channels and NMDA receptors underlie this altered dendritic integration. Using dendritic recordings and Ca^{2+} imaging, it has been possible to demonstrate an increase in excitability that was spatially restricted to the dendritic subcompartment that received the potentiated synaptic input (Johnston et al., 2003; Frick et al., 2004). This was expressed as an altered shape of the EPSPs (Frick et al., 2002), an increase in bAPs and in their associated Ca^{2+} signal, and a reduction in the A-type K^+ current. Because this current has a dampening influence on dendritic excitability (Hoffman et al., 1997; Bekkers, 2000), such modulation would be expected to directly increase the amplitude and summation of EPSPs, and to improve the impact of other inward currents (Na^+ and Ca^{2+} channels) on EPSP integration. These changes in dendritic excitability are likely to affect the generation of dendritic Na^+ and/or Ca^{2+} spikes (Andreasen and Lambert, 1995; Golding and Spruston, 1998; Magee and Carruth, 1999). This form of plasticity may also have behavioral significance; for example, dendritic recordings from Purkinje cells in cerebellar slices from rats that underwent delay eye-blink conditioning demonstrate a reduced threshold for dendritic calcium spike initiation (Schreurs et al., 1997, 1998).

Together, these studies indicate that synaptic integration is dependent on the prior activity of the neuron, and that some forms of intrinsic plasticity can be induced concomitantly, and function synergistically with changes in synaptic strength. Spatially restricted forms of intrinsic plasticity (see also Yasuda et al., 2003) may be accompanied or counterbalanced by more global changes in excitability to keep the neuron in its optimal operating range (Stemmler and Koch, 1999; Fricker and Johnston, 2001; Turrigiano and Nelson, 2000; Häusser and Mel, 2003).

Intrinsic Plasticity and Epilepsy

In addition to physiological activity patterns, pathological conditions such as epileptic activity, chronic stress, drug abuse, and dementia can lead to alterations in neuronal excitability. In this section, we focus on changes in dendritic excitability occurring in response to various experimental models of epilepsy. In these models, the activity of various serine-threonine and tyrosine kinases is upregulated (Chen et al., 1992; Garrido et al., 1998), potentially leading to a modulation of a number of voltage-gated Na^+, K^+, and Ca^{2+} channels in the soma and dendrites. However, it should be noted that the activation of protein kinases and phosphatases, albeit a powerful mechanism, is not the lone factor altering intrinsic excitability.

In experimental models of epilepsy, modulation of ion channels has been reported (Chen et al., 2001; Su et al., 2002). In the pilocarpine model of chronic temporal lobe epilepsy (that mimics many aspects of the human disorder), an acquired channelopathy of A-type K^+ channels in CA1 pyramidal neurons of rats was recently reported [Table 1 and Fig. 2(C); Bernard et al., 2004]. This A-type K^+ current was reduced due to a partial loss of the underlying Kv4.2 channel subunits, and to the modification of the remaining channels by ERK phosphorylation. As a result, the dendritic excitability of CA1 pyramidal neurons was increased, thereby enhancing the back-propagation of APs. In the absence of compensatory mechanisms, an increased Ca^{2+} influx from larger bAPs and an enhanced synaptic integration would be expected to occur as well (Hoffmann et al., 1997; Ramakers and Storm, 2002; Frick et al., 2004). The same experimental model of epilepsy has been found to cause a large fraction of CA1 pyramidal neurons to convert from regular firing to a burst-firing mode (Sanabria et al., 2001). Burst-firing is a biophysical property of neurons that likely involves the activation or de-/inactivation of somatic and dendritic voltage-gated conductances such as Na^+, Ni-sensitive Ca^{2+}, A-type K^+, or D-type K^+ channels (Golding et al., 1999; Magee and Carruth, 1999; Jung et al., 2001), suggesting that epilepsy causes a modulation of these channels. This switch to a bursting mode will result in a strong alteration of the input–output function of individual neurons, and therefore augment the output from the hippocampal networks (Lisman, 1997). Bursting neurons could function as pacemakers in the

generation of epileptiform activity in the acute and chronic stages of the disorder (Sanabria et al., 2001).

In a kainate model of chronic temporal lobe epilepsy, Misonou and colleagues show that seizure activity modulates Kv2.1 channels *in vivo* (Misonou et al., 2004). Kv2.1 channels, which mediate delayed rectifier K^+ currents, are typically expressed in large clusters on the somata and proximal dendrites of hippocampal and neocortical pyramidal neurons. Seizure activity abolished this clustered organization and decreased the phosphorylation state of Kv2.1 channels, thereby presumably altering their biophysical properties and their effectiveness in controlling membrane excitability. Shah and colleagues (2004), in the kainate model of acute epilepsy, recently demonstrated a reduction of I_h in dendrites of layer III neurons in the entorhinal cortex. These and other studies thus suggest that both acute and chronic changes in dendritic ion channels may play an important role in the development of seizure disorders.

CONSEQUENCES OF INTRINSIC PLASTICITY

Does Intrinsic Plasticity Play a Role in Learning and Memory?

A prerequisite for a long-term memory mechanism is the persistence of information storage (Dudai, 2002). Several invertebrate and vertebrate studies link enduring changes in neuronal excitability to specific learning tasks (see Intrinsic Plasticity Induced by Learning Tasks; Brons and Woody, 1980; Alkon et al., 1982; Alkon, 1984; Alkon et al., 1985; Schreurs et al., 1997, 1998). The conclusion from these studies is that intrinsic plasticity could, in some learning paradigms, fulfill the criterion of persistence.

An alternative interpretation is that intrinsic plasticity does not constitute the engram itself, but instead plays a permissive, or supportive role in establishing memory traces (Zhang and Linden, 2003). Several arguments attest to this view: First, some learning tasks (e.g., trace eye-blink conditioning; Disterhoft et al., 1986; Coulter et al., 1989; de Jonge et al., 1990; Moyer et al., 1996; Thompson et al., 1996) might increase the excitability of a large fraction of neurons ($> 50\%$) within the network involved in the learned task. This renders the storage of specific memories in the functional state of channels unlikely, and rather points to a role of intrinsic plasticity in enhancing the overall excitability of this particular network to improve learning of the specific task. Second, while learning tasks typically produce enduring memories, some forms of intrinsic plasticity may be temporary (hours to days). This has been shown for trace eye-blink conditioning in the hippocampus (Disterhoft et al., 1986; Coulter et al., 1989; de Jonge et al., 1990; Moyer et al., 1996; Thompson et al., 1996), operant conditioning in the piriform cortex (Saar et al., 1998, 2001), and Pavlovian conditioning in the amygdala (Rosenkranz, personal communication). An increased neuronal excitability could thus promote other activity-dependent modifications (e.g., synaptic plasticity) during the same time window (Moyer et al., 1996; Saar and Barkai, 1998; Rosenkranz and Grace, 2002). This permissive, or supportive function of intrinsic plasticity has also been implicated in savings and rule learning (Brons and Woody, 1980; Saar and Barkai, 2003; Zhang and Linden, 2003). Rule learning is defined here as the ability to acquire new memories in a more efficient and rapid manner following learning of similar tasks. For instance, in an operant conditioning task, rats are more capable of discriminating between pairs of odors once they have learned the discrimination task for a first pair. This improved learning persists for 5 to 7 days and correlates well with a temporary decrease in the postburst amplitude of the AHP in pyramidal neurons of the piriform cortex (reviewed in Saar and Barkai, 2003). Without further training, the AHP amplitude returns to control values and rats no longer discriminate more efficiently between new odor pairs. However, the behavioral memory for the initial discrimination is not impaired. Evidence for a role of intrinsic plasticity in savings has been found following associative conditioning in cats (Brons and Woody, 1980). When the conditioned response was extinguished by repeated presentations of the conditional stimulus by itself, the increase in excitability was not abolished. In addition, retraining resulted in a faster rate of learning of the conditioned response, suggesting a role for intrinsic plasticity in this process.

Could Intrinsic Plasticity Increase the Storage Capacity?

Another distinctive attribute for a cellular memory mechanism is the input- or synapse-specificity of information storage. Long-term changes in synaptic strength (LTP, LTD) are computationally appealing models for memory storage because they allow synapse-specific changes among a large number of inputs. In this view, the potential storage capacity of a neuron is large, because information can be stored independently in every synapse, for example, in the

order of 10^4 per neuron (for CA1 or neocortical pyramidal neurons; Mel, 1999; Poirazi and Mel, 2001). Whether intrinsic plasticity can increase or decrease the storage capacity, or modify the quality of the storage of information will primarily depend on the location and spatial restriction of this plasticity. Consider a modulation in the region of the AP initiation site; in this scenario, the efficacy of the majority of synapses to contribute to neuronal AP output may be altered, leading to a more global regulation of activity levels. This mechanism would likely dramatically lower the storage capacity of a neuron. In contrast, intrinsic plasticity could be spatially restricted to the scale of dendritic subcompartments, or even to single synaptic connections (Johnston et al., 2003; Yasuda et al., 2003; Frick et al., 2004). Theoretical studies suggest that this would provide the neuron with an additional tier of regulation, possibly increasing the storage capacity (Mel, 1999; Poirazi and Mel, 2001). Information stored in channels within a dendritic region larger than a single synapse, but smaller than the whole dendrite, would alter the computation performed by this module and the quality of the stored information (Poirazi et al., 2003). Some forms of memory, such as declarative memory, may benefit by the high degree of specificity conferred by plasticity of a single synapse. Other forms, such as nondeclarative memory, may benefit from the relative nonspecificity of intrinsic plasticity of a dendritic module (Zhang and Linden, 2003).

Dendritic Excitability as a Substrate for Metaplasticity?

The implications of intrinsic plasticity in savings and rule learning'in behavioral learning tasks were discussed above. On a cellular level, an important question is how does intrinsic plasticity in the dendrites prime the neuron to undergo further plasticity, a phenomenon referred to as metaplasticity (Abraham and Bear, 1996). Synaptic plasticity is largely a dendritic feature, because the integrative properties of dendrites provide the basis for properties such as associativity and cooperativity between synaptic inputs (Mainen, 1999; Sjöstrom et al., 2001; Häusser and Mel, 2003; Poirazi et al., 2003). Therefore, plasticity of dendritic excitability has important consequences for the computational capacity of the dendrites as well as for the rules that govern synaptic plasticity. As discussed above, behavioral learning, pathological conditions such as epilepsy, or activity can trigger alterations of various dendritic conductances. Such changes will modulate the computational capabilities of the dendrites, modifying the amount of associativity and cooperativity of synaptic inputs necessary to induce synaptic plasticity. Furthermore, short trains of bAPs have been demonstrated to induce an enduring depression of R-type Ca^{2+} channels in individual spines, thereby inhibiting the induction of subsequent synaptic plasticity (Yasuda et al., 2003). In addition, the important link between bAPs and the induction of associative plasticity renders the tuning of AP back-propagation a crucial substrate for metaplasticity. For example, an enhanced dendritic invasion by bAPs (Tsubokawa et al., 2000; Quirk et al., 2001; Bernard et al., 2004; Frick et al., 2004) will provide stronger depolarization of this dendritic area and increase the associated Ca^{2+} influx. As a result, synaptic input paired with bAPs will experience regional differences in depolarization/Ca^{2+} influx, due to the decline and frequency-dependent attenuation of bAP amplitudes. Furthermore, this may influence the magnitude, direction, and the spatial extent of synaptic plasticity (Magee and Johnston, 1997; Markram and Sakmann, 1997; Sourdet and Debanne, 1999; Bi and Poo, 2001; Sjöstrom and Nelson, 2002; Watanabe et al., 2002). The spatial extent of dendritic intrinsic plasticity could provide a means for spreading such forms of metaplasticity to neighboring synapses or branches, eventually requiring compensatory homeostatic mechanisms (Abbott and Nelson, 2000; Turrigiano and Nelson, 2000; Marder and Prinz, 2002).

CONCLUSIONS AND PERSPECTIVE

In summary, there are numerous examples of activity-dependent regulations of the intrinsic excitability of neurons *in vivo* and *in vitro*, stressing the importance of an additional dimension for plasticity. This plasticity might regionally regulate the properties or expression levels of ion channels, for example, at synaptic contacts, the parent dendrites or in the axon, thereby altering the integrative properties of these structures. Thus, the initiation, summation and propagation of signals in the neuron will be shaped by intrinsic plasticity, perhaps optimizing information transfer and firing rates. Conversely, intrinsic plasticity could also potentially counteract, or exacerbate pathological conditions. Many questions in this relatively unexplored field are now open for investigation—on a mechanistic as well as functional level. For example, what are the underlying induction and expression mechanisms for alterations in intrinsic excitability? How persistent is intrinsic plasticity, and

what is its role in the behaving animal? To determine how the various mechanisms of plasticity fulfill different roles, and at the same time cooperate in regulating complex tasks such as development, adaptation, and information storage, will be a great challenge for the future.

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