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Plasticity of dendritic function

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The various properties of neuronal dendrites — their morphology, active membrane and synaptic properties — all play important roles in determining the functional capabilities of central nervous system neurons. Because of their fundamental involvement in both synaptic integration and synaptic plasticity, the active dendritic properties are important for both neuronal information processing and storage. The active properties of dendrites are determined by the densities of voltage-gated ion channels located within the dendrites in addition to the biophysical characteristics of those channels. The real power of this system resides in the level of plasticity that is provided by the many forms of channel modulation known to exist in neurons. Indeed, voltage gated ion channel modulation shapes the active properties of neuronal dendrites to specific conditions, thus tailoring the functional role of the single neuron within its circuit.

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Introduction

Voltage-gated ion channels in dendrites are important in establishing the processing and storage of information in neurons. These channels shape the integration of incoming synaptic input and in turn determine the pattern of action potential output through a complicated interplay with neuron morphology and synaptic properties. Furthermore, the active properties of dendrites are intricately involved in both the induction and the expression of various forms of synaptic and non-synaptic (intrinsic excitability) plasticity.

Central nervous system (CNS) neurons exhibit a large variety of dendritic morphologies, and there seems to be at least as many different ion channel distributions as there are different arborizations [1,2]. There are, in fact, significant differences in dendritic channel complements even within general classes of neurons (e.g. cortical versus hippocampal pyramidal neurons). In spite of this variability, some general statements can be made, with exceptions of course. Most arbors contain some types of Na^+ (Purkinje cells do not), K^+ and Ca^{2+} channels and most cells also have hyperpolarization-activated (dentate granule cells do not) and inward rectifying K^+ channels in their dendrites. The wide range of functional properties displayed by CNS neurons largely stems from heterogeneous distributions of channel subtypes and the modulatory systems that regulate them.

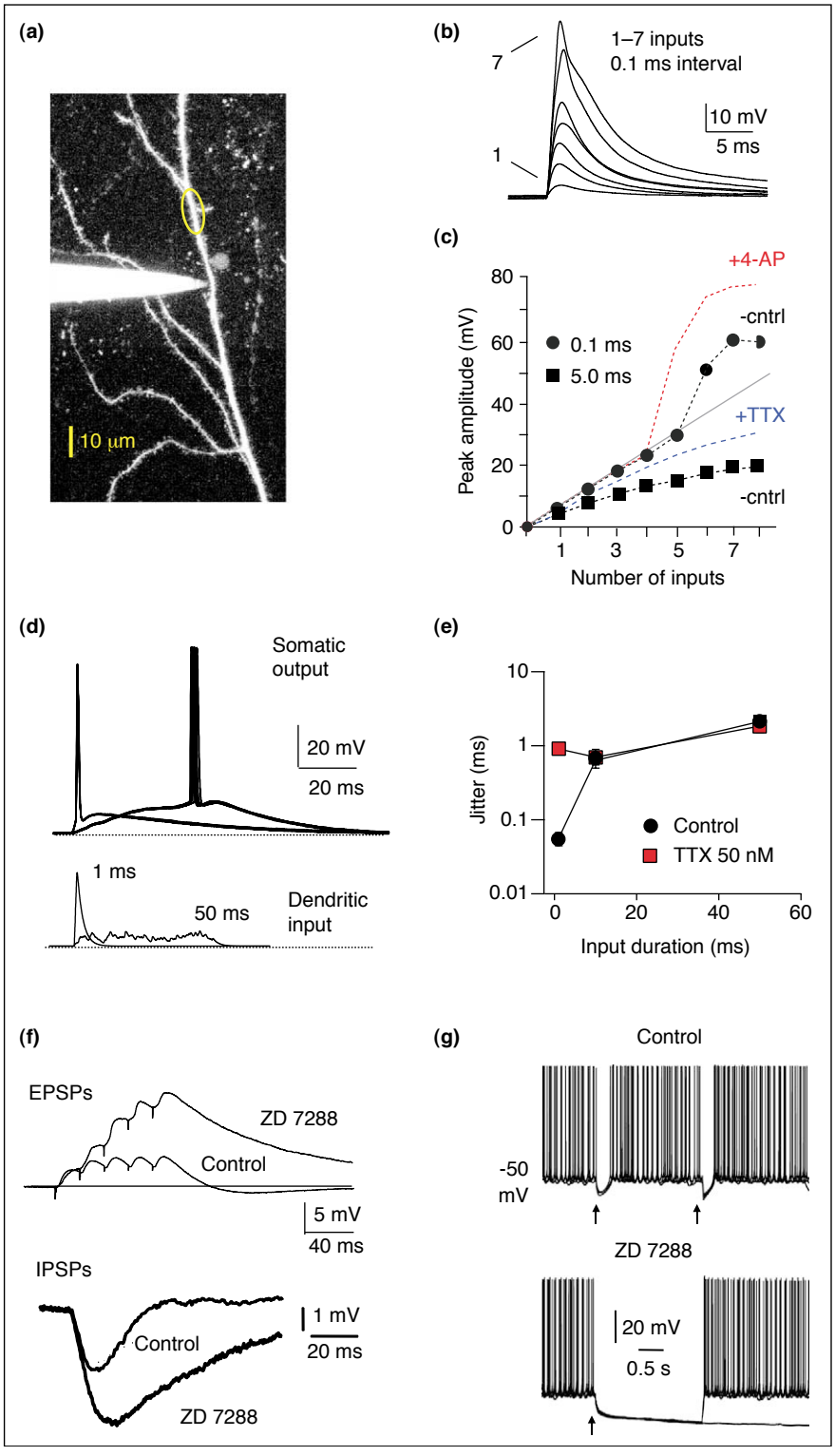
One of the more advantageous properties of voltage-gated ion channels is the ease with which their fundamental properties (various voltage dependencies) and densities can be modulated. This ability to modify the active dendritic properties enables neurons to change the way they process and store information dynamically, transforming the computational role of a neuron within its particular network. Below we give some brief examples of how dendritic voltage-gated ion channels shape synaptic integration and plasticity, and then discuss how modification of the properties of these dendritic channels can affect neuronal function on wide-ranging time scales.

Dendritic integration

Na^+ -K^+ -Ca^{2+} channels

Pyramidal cell dendrites contain a population of Na^+ and K^+ channels that help to produce either a linear or a non-linear dendritic integration mode [3–6,7••,8•,9,10•]. In CA1 and perhaps layer V pyramidal neurons, spatio-temporally dispersed input patterns activate dendritic Na^+ and K^+ channels in a way that produces a linear type of dendritic summation (Figure 1c; squares) [7••,8•,9,10•]. In this linear integration mode, action potential output frequency (in addition to coarse timing) is a direct function of the relative amounts of excitatory and inhibitory input, with increases in excitatory drive elevating firing frequency and in some cases reducing spike latency [7••,9]. There is of course a level of membrane depolarization at which Na^+ channel activation can become regenerative, leading to the local initiation of a dendritic spike [3,6,7••,8•,9,10•,11] (Purkinje cells use their rapidly activating P/Q Ca^{2+} channels [12]). In pyramidal neurons, this local spike generation usually requires a relatively large and fast dendritic depolarization, and it shifts the integration mode to highly supra-linear (Figure 1b,c;) [3,6,7••,8•,9,10•,11]. The exact shape (amplitude and duration) of the dendritic spike initiated is important because it will, in turn, determine the form of action potential output by the axon in the non-linear integration

Figure 1



Dendritic channels shape synaptic integration and action potential output. **(a)** Image of CA1 dendrite showing recording location and input site. **(b)** Dendritic depolarizations induced by progressively larger amounts of synchronous input eventually lead to the initiation of a dendritic spike. **(c)** Plot of dendritic membrane potential (Vm) in response to increasing amounts of asynchronous (5 ms) and synchronous (0.1 ms) input patterns, demonstrating linear and supra-linear summation, respectively. The plot also shows that block of Na^+ channels with TTX prevents non-linearity (blue line), whereas block of K^+ channels with 4-AP decreases threshold (red line). **(d)** Spike output patterns in response to asynchronous (all input in 50 ms) or synchronous (all input in 1 ms) input patterns. **(e)** Plot of variation in action potential output timing for the different patterns. Low (50 nM) [TTX] inhibits dendritic spike propagation and removes the sharp reduction in output jitter produced by synchronous input patterns. **(f)** Blockade of Ih greatly increases the summation of both excitatory and inhibitory input in pyramidal cells. **(g)** Ih blockade enhances the ability of transient inhibitory input to reduce ongoing action potential output in Purkinje cells. Figure adapted with permission from [9] (c), [10•] (d,e), [14] (f) and [16] (g).

mode. If, as is usually the case in CA1 pyramidal neurons, a mainly fast Na^+ spike is generated in the dendrites, its impact on the output state will primarily be through the initiation of a single well-timed high-precision action potential in the axon (assuming forward propagation is robust; Figure 1d,e; 1 ms input) [9–11]. At the other extreme, local spikes (or large synaptic events) can trigger regenerative Ca^{2+} channel activation and the production of Ca^{2+}-plateau potentials (N-methyl-D-aspartate receptors [NMDARs] can also support slow, plateau potentials) [6,8•,12]. These plateaus give a large boost to the synaptic input and also provide a depolarizing envelope that drives the burst firing of several high frequency Na^+ spikes. In some cells or conditions a combination of fast Na^+ and slow Ca^{2+} spikes is generated, and in this case a well-timed burst of output spikes is produced [6,13]. This ability of dendritic channels to produce either a linear or a non-linear integration mode and the unique output pattern associated with each increases the computational range of neurons and could play an important part in the generation of specific behaviors.

Hyperpolarization-activated channels

Another channel type that profoundly affects dendritic integration in a variety of neurons is the hyperpolarization-activated channel (Ih), which is densely expressed in Purkinje cells and most types of pyramidal neurons [1,2]. These channels are active at most resting membrane potentials and further hyperpolarization increases their activity. The current produced by the activation and deactivation of these channels shapes temporal summation of synaptic input and limits the impact of both excitatory and inhibitory drive [14,15] (Figure 1f). In pyramidal neurons, this reduces the influence of synapse location on temporal summation and action potential output pattern and, in Purkinje cells, it limits the ability of synchronous inhibitory input to slow constitutive firing [14–16] (Figure 1g). Genetic deletion of these channels has led to some very interesting behavioral deficits that can be linked to alterations in the integrative properties of both of these neurons [17,18••]. Thus, it is clear that the specific input–output transformation occurring in a given cell will depend greatly on the exact complement of ion channels present in its dendritic arbor.

Synaptic plasticity

Na^+ -K^+ -Ca^{2+} channels

The voltage-gated ion channels in the dendrites of pyramidal neurons enable them to not only forward propagate dendrite-initiated spikes but also to back-propagate action potentials that were initiated in the axon. This back-propagating action potential (bAP) is an effective feedback signal providing the input region with information about the output state of the neuron [19,20]. Indeed, bAPs appear to function as an induction mechanism in several forms of associative synaptic plasticity [19,21,22•]. One attractive feature provided by the bAP is a timing-dependence. There have been reports in a variety of preparations that the Ca^{2+} signals associated with the bAP and the synaptic input sum supra-linearly when the timing of the two events is coincident within a fairly tight window (<50 ms) [22•] (Figure 2a,b). This interaction between input and output enables spikes that follow synaptic input within a few tens of milliseconds to produce a postsynaptic Ca^{2+} signal that is larger than if the spike preceded the input or if it lagged too far behind (>50 ms). This timing dependence is likely to be mediated by both NMDA receptor and voltage-gated ion channel mechanisms, and is a candidate mechanism for aspects of spike-timing dependent plasticity (STDP) [21,22•,23].

Local dendritic spikes are also involved in the induction of non-Hebbian forms of synaptic plasticity; that is, no associated action potential output is necessary for their induction [24,25•]. The large Ca^{2+} influx that accompanies the poorly propagating local dendritic spikes is mediated by both voltage-gated Ca^{2+} channels and NMDA receptors, and seems to be capable of inducing a long lasting alteration in the synaptic weight. Thus, the presence of dendritic voltage-gated ion channels enables dendrites to produce both forward and backward propagating spikes that, if properly timed, contribute to the local synaptic depolarization and subsequent Ca^{2+} influx. This, in turn, leads to the activation of the various signaling pathways that underlie the alterations involved in the regulation of synaptic weight.

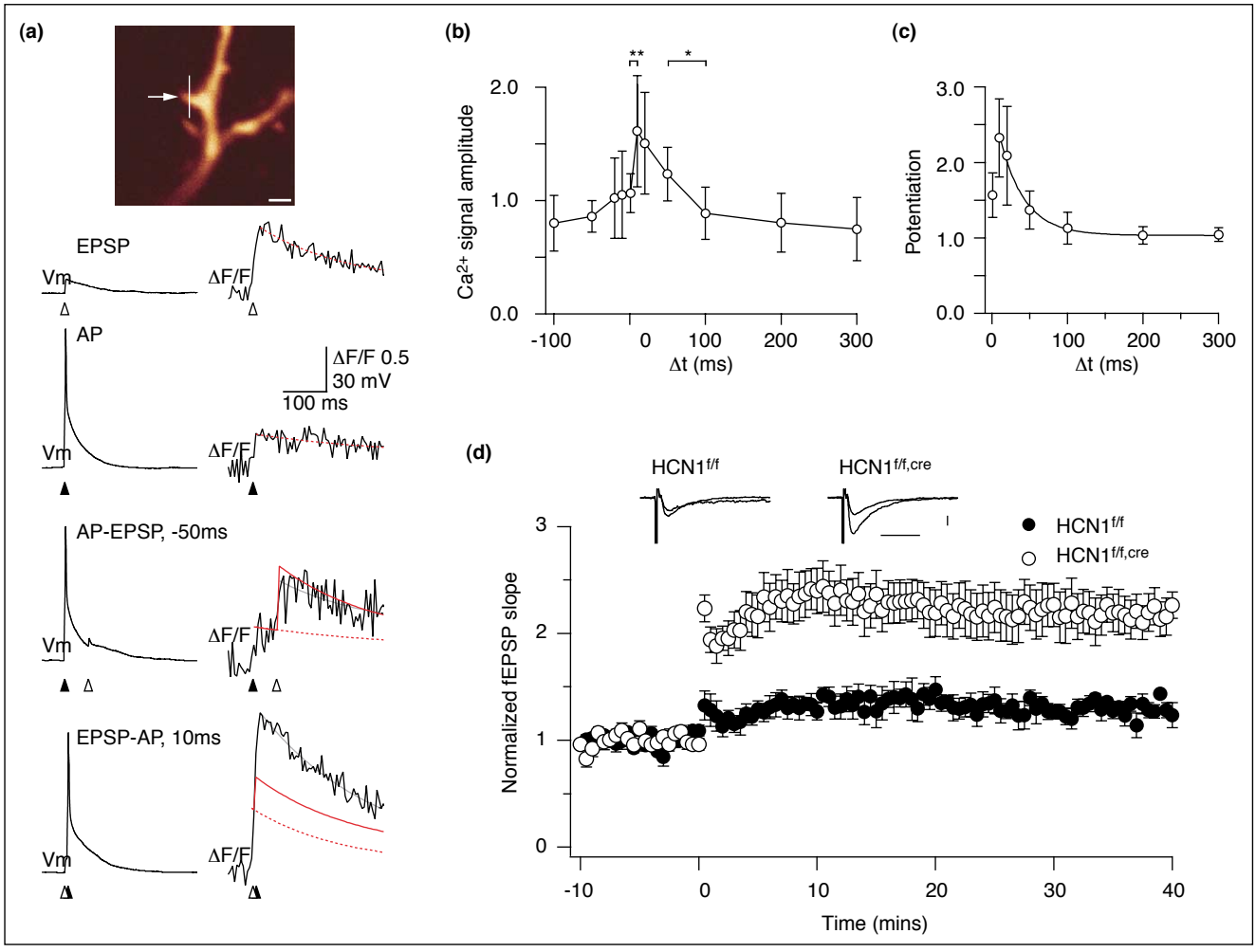
Hyperpolarization-activated channels

In those neurons where Ih is heavily expressed, usually in the distal dendritic regions, the summation of spatio-temporally distributed inputs is inhibited by H-channel deactivation. The reduction of local synaptic summation leads to lower levels of dendritic depolarization and associated Ca^{2+} influx [14]. This H-channel mediated decrease in input summation also reduces the expression of some forms of synaptic plasticity (perforant path LTP in CA1, see Figure 2c), thus endowing H-channels with a unique ability to regulate the efficacy of distal input pathways in a way that appears to be behaviorally significant [18••].

Regulation of dendritic function

We have seen above that by shaping the integration of incoming synaptic input and by providing both associative and non-associative Ca^{2+} influx mechanisms, the active properties of dendrites are heavily involved in determining the impact of a given synaptic input. One advantage of a system governed by voltage-gated ion channels is the level of flexibility it provides. Because the channels themselves are so easily and widely modulated (voltage-ranges and kinetics of activation and inactivation in addition to channel subunit composition and density), the dendritic integration of incoming synaptic

Figure 2



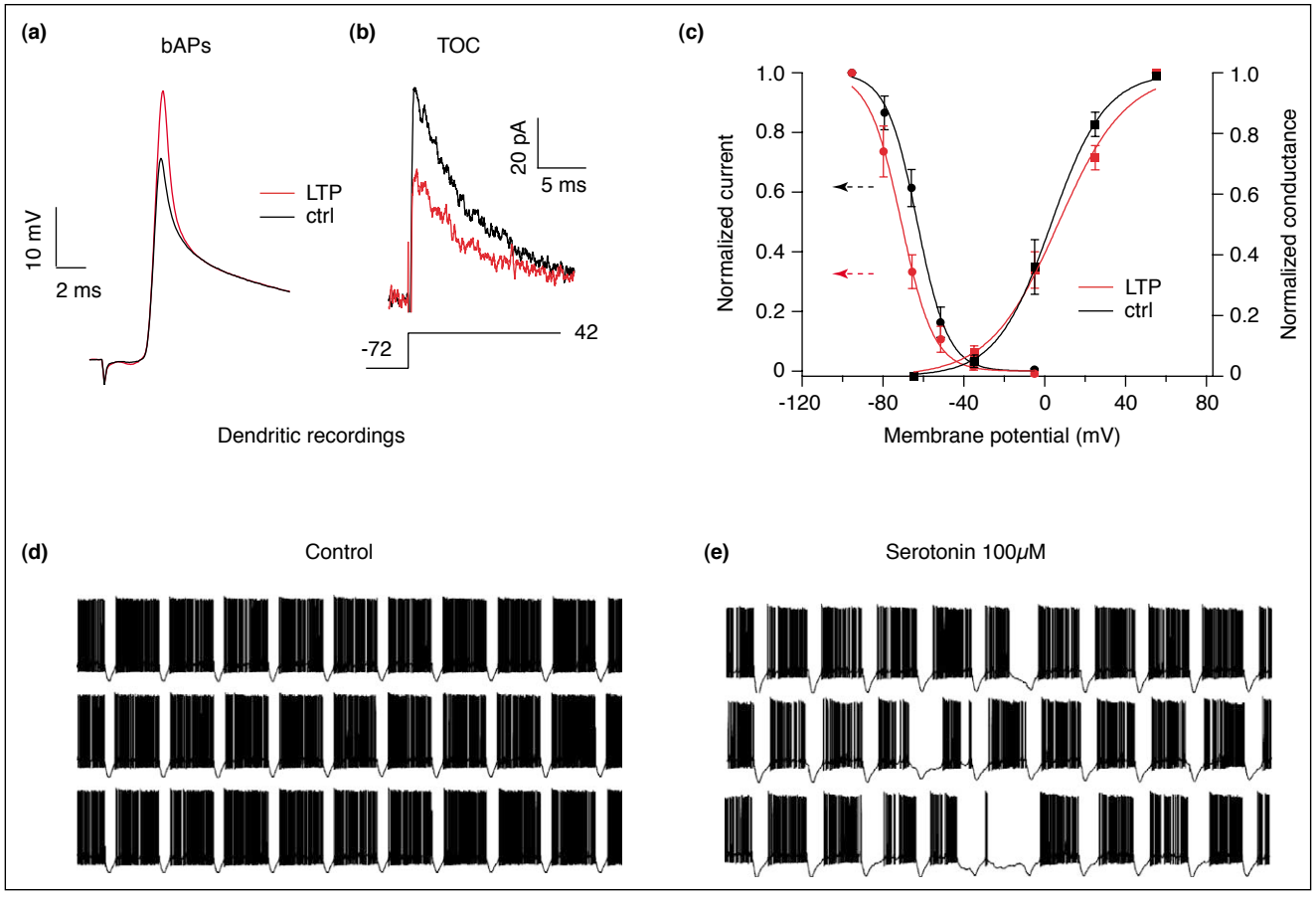
The role of dendritic channels in synaptic plasticity. **(a)** An image of a dendrite and a spine in which correctly timed synaptic input and action potential output produce Ca^{2+} signals that sum supra-linearly. **(b)** A plot of Ca^{2+} signal amplitude versus excitatory postsynaptic potential–action potential (EPSP–AP) timing, showing the timing dependence of the Ca^{2+} signal. **(c)** Plot of timing dependence of EPSP–AP pairing-induced synaptic potentiation. Note the similarity to the Ca^{2+} signal timing dependence. **(d)** Plot showing that LTP of entorhinal input to CA1 is enhanced in mice that have Ih (HCN1) genetically deleted. Figure adapted with permission from [22•] (a-c) and [18••] (d).

input can vary from one condition to another very quickly, in addition to being altered for long periods of time. This enables information to be stored by the pattern of dendritic membrane excitability and permits the neuron to perform the most appropriate computation for a given behavioral state. We have loosely divided the regulation of dendritic function through ion channel modulation into groups based on the time course of the modifications (transient, prolonged and persistent), with each form associated with different but overlapping functions.

Transient channel modulation

The most transient form of modulation involves the normal voltage-dependent inactivation of various ion channels by different activity patterns (both spiking patterns and subthreshold membrane fluctuations). Such changes in channel inactivation can alter the excitability of dendrites within just a few milliseconds of a brief depolarizing event and last for up to several seconds thereafter, depending on the time course of recovery from inactivation. For example, membrane potential oscillations at theta frequencies (4–9 Hz) can lead to increases in bAP amplitudes and durations at different phases of the cycle [20,26]. The mechanisms for this appear to be mediated through changes in inactivation of A-type K^+ channels and activation of Na^+ and other K^+ channels. Moreover, a slow mode of Na^+ channel inactivation [27,28] causes the refractory period for bAPs to be as long as several seconds, reducing significantly the propagation of subsequent bAPs.

Figure 3



Modulation of dendritic voltage-gated ion channels. **(a)** The amplitude of backpropagating action potentials is increased in the apical dendrites following LTP induction in CA1 pyramidal neurons. **(b)** Transient outward current (TOC) amplitude evoked from resting membrane potentials is reduced because of a hyperpolarizing shift in the inactivation curve following LTP induction **(c)**. The reduced channel availability at resting potentials results in the increase in bAP amplitude. **(d)** Brief inhibitory input causes short pauses in spontaneous Purkinje cell action potential output under control conditions. **(e)** Application of serotonin causes a large increase in the inhibition of action potential output that is consistent with a negative modulation of Ih channel activity by serotonin. Figure adapted with permission from [38•] (a-c) and [16] (d,e).

Another transient form of channel modulation is that associated with the presence of neuromodulatory inputs and lasts for only as long as the modulator is present. General examples of this form of modulation are those modifications in dendritic active properties that occur during normal behaviorally related shifts in neuromodulatory state (Figure 3d,e). All known dendritic voltage-gated ion channels show significant modulation by one or more neurotransmitter systems, including aminergic (NE, 5HT, DA), cholinergic (mACh), glutamatergic (mGluR), GABAergic (GABAb) and lipid messengers (AA, PGE2, PIP2) [29–33]. The specific channel effects of these modulators depend not only on the particular ion channel involved but also on the subcellular receptor subtype distribution. Thus, 5HT can have both an inhibitory and an enhancing effect on Ih depending on whether 5HT1a or 5HT4 receptors are activated [32]. Indeed, there are reports of different subcellular receptor distributions within a single cell in addition to specific innervation patterns [32]. To further complicate things, the exact effect of any given modulator can depend on the modulator concentration and duration and on the level of concurrent neuronal activity [33]. Because of this complexity we are probably not at a point at which one particular effect on dendritic processing can be ascribed to any given neuromodulatory pathway.

Prolonged channel modulation

Prolonged alterations outlast the presence of a specific neuromodulator or specific pattern of input [34]. This type of modulation would be found in the longer-lasting changes in dendritic channel properties that are induced by certain behavioral paradigms and/or long-term potentiation (LTP) or long-term depression (LTD) induction protocols. Examples of this form of plasticity have been found both in hippocampal and in cerebellar neurons,

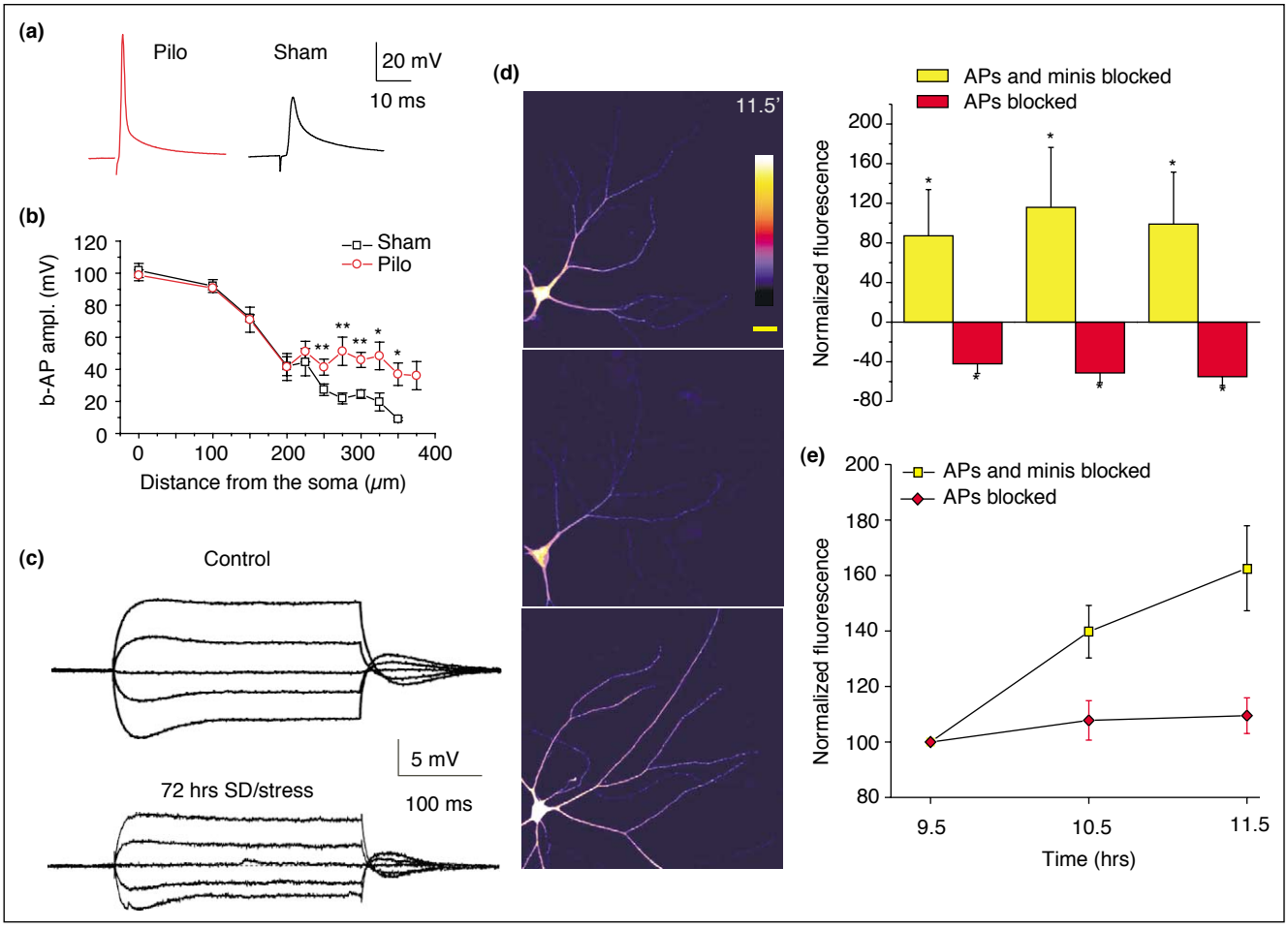
where the activation of kinase signaling pathways (PKA, PKC, MAPK) by LTP-inducing synaptic input patterns leads to the expression of both long-term synaptic plasticity and long-term modulation of specific dendritic ion channels [35–37,38•,39] (Figure 3a–c).

The induction of long-term changes in active dendritic properties is not limited to synaptic input protocols, but can also follow increased postsynaptic action potential firing and particular forms of channel modulation [40,41••]. There are also reports of interesting interactions between synaptic input patterns and neuromodulator application. Indeed, the presence of particular amines (dopamine [DA], norepinephrine [NE]) enhances the ability of certain input patterns to induce LTP, and such interactions have been proposed as mechanisms for the memory-enhancing powers of attention [42,43]. Thus, the combined effect of synaptic input patterns and neuromodulator receptor activation might be particularly effective in producing alterations in the weight of a given synaptic input, and in the mode in which it is integrated in the dendrites. Taken together, these long-term modifications could provide the neuron with a highly effective information storage mechanism.

Persistent channel modifications

Persistent modifications are responsible for long-term regulation of the input–output characteristics of a neuron and involve slow changes in dendritic channel densities or subunit composition through either alterations in gene expression or in protein recycling. These are the adaptive types of changes that are responsible for establishing the various subcellular voltage-gated ion channel distributions that exist under normal conditions and the maladaptive alterations observed to occur in a growing list of pathological situations (for example, epilepsy, sleep

Figure 4



Persistent dendritic channel modifications. **(a,b)** Action potential backpropagation in hippocampal CA1 pyramidal neurons is elevated following the experimental induction of epilepsy (pilocarpine injection). This enhanced propagation is probably the result of a decrease in dendritic Kv4.2 channel activity. **(c)** Dendritic input resistance in CA1 cells is reduced following a sleep deprivation protocol because of an alteration in dendritic Ih channels. **(d,e)** Experiments showing that dendritic protein synthesis is regulated by spontaneous synaptic activity (minis). Figure adapted with permission from [44] (a,b), [45] (c) and [52••] (d,e).

deprivation and axon transection, see Figure 4a,b) [44–46,47,48•]. To date, little is known about the signaling pathways involved in this form of channel regulation or even the degree to which it is modifiable [34]. Most available evidence, however, points to some interaction with the overall electrical activity of the neuron, thus implicating intracellular Ca^{2+} and associated biochemical pathways [49,50]. Another interesting mechanism is local dendritic protein synthesis. There are several reports that mRNA translation and local dendritic protein synthesis are regulated by synaptic input and postsynaptic activity [51,52••] (Figure 4c). Although most of the studies to date have examined the role of local protein synthesis and degradation in the activity-dependent regulation of synaptic modifications, this same system is likely to be involved in the long-term regulation of voltage-gated ion channel composition and density.

Conclusions

The specific active properties of dendritic arbors profoundly shape the computational and storage capabilities of single neurons. As discussed above, modification of these properties provides the neuron with a degree of flexibility that enables it to perform the most appropriate computation for a given condition. Conversely, it also provides an opportunity for mis-relations between the active dendritic properties and a particular behavioral state to produce various pathological conditions.

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