Review

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Historical perspective

Active dendrites: colorful wings of the mysterious butterflies

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Santiago Ramón y Cajal had referred to neurons as the 'mysterious butterflies of the soul.' Wings of these butterflies – their dendrites – were traditionally considered as passive integrators of synaptic information. Owing to a growing body of experimental evidence, it is now widely accepted that these wings are colorful, endowed with a plethora of active conductances, with each family of these butterflies made of distinct hues and shades. Furthermore, rapidly evolving recent literature also provides direct and indirect demonstrations for activity-dependent plasticity of these active conductances, pointing toward chameleonic adaptability in these hues. These experimental findings firmly establish the immense computational power of a single neuron, and thus constitute a turning point toward the understanding of various aspects of neuronal information processing. In this brief historical perspective, we track important milestones in the chameleonic transmogrification of these mysterious butterflies.

Background for active dendrites

In 1993, Stuart, Dodt and Sakmann [1] published a landmark paper in which they used a new technique for visualizing neuronal dendrites in living brain slices to record, with whole-cell patch electrodes, action potentials in dendrites of neocortical pyramidal neurons. A year later, Stuart and Sakmann [2] used this technique to make dual recordings from the soma and dendrite of neocortical layer 5 pyramidal neurons and showed unequivocally that action potentials initiated in the axon/soma region could propagate (called backpropagation) into the dendrites. This paper was the first direct demonstration that dendrites possess the voltage-gated ion channels necessary for sustaining action potential propagation, and is widely thought to have ushered in a new era for the investigation of active dendrites. Although the importance of this paper cannot be overstated for both the introduction of new technology for visualized patch-clamp recordings from dendrites as well as for beginning a new direction for research into the function of dendrites, it is worth taking a step back to put this work into the perspective of the prior experiments and ideas of others, and in particular the seminal work by Rodolfo Llinás [3–7], which provided the foundation for this field at the time of the publication of this important paper (see also Refs [8–10]).

Although the processes of nerve cells that would later be called dendrites (the term 'dendrite' was coined by Wilhelm His [11]) were shown in sketches by several workers in the early 1800s, the first detailed description of dendrites came from Golgi in 1873 [12] after his revolutionary development of the silver stain. He called them 'protoplasmic prolongations' and viewed them (albeit incorrectly) as serving a nutrient role for neurons. Cajal [13] later introduced what would become known as the Neuron Doctrine (see Ref. [14]), which hypothesized that neurons were self-contained units of the nervous system with dendrites serving as the main input site for information that flowed from dendrites through the soma and outputting to other neurons along its axon. With the advent of surface recordings from the cortex in the 1940s, there became a lively debate for many years about whether dendrites reflected stationary, graded potentials in these surface recordings or the active propagation of electrical signals. With few exceptions, the prevailing view at the time was that the action potential was initiated in the axon hillock and propagated via the axon into the synaptic terminals (reviewed in Ref. [15]). Dendritic membrane was considered incapable of active propagation of electrical signals, serving only as a passive integrator of excitatory and inhibitory synaptic input. A mathematical theory for how this dendritic integration might work was provided by the seminal papers by Wilfred Rall beginning in 1957 (see Ref. [16]).

Several chinks in the armor of this prevailing view, however, began to appear in the late 1950s and 1960s. From the interpretation of extracellular field recordings, several studies suggested that action potentials might actively propagate through dendrites [17–20]. In a landmark paper by Kandel and Spencer [21], small, spike-like potentials (called fast pre-potentials) were recorded intracellularly with microelectrodes from hippocampal pyramidal neurons *in vivo* and hypothesized to be action potentials that had originated in dendrites. In the 1970s, improved intracellular, microelectrode techniques and *in vitro* brain slice preparations became available. Although difficult and rare, direct intracellular recordings from dendrites with microelectrodes were possible. Such dendritic recordings revealed action potentials in dendrites of cerebellar Purkinje cells and cortical and hippocampal pyramidal neurons [3,22–25]. Theories also began to appear about how active dendrites might participate in dendritic signaling [26–28].

From the intracellular recordings of dendritic spikes with sharp microelectrodes by Llinás, Wong and others to the multiple, whole-cell recordings of spike backpropagation in

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dendrites of Stuart and Sakmann, it has been clear for some time that dendrites are not passive integrators of synaptic inputs. During the past 15 years or so there has been a rapid explosion of new information about dendrites such that the extent to which dendrites have proven to be 'active,' and the complicated ways in which these active properties regulate synaptic integration and single-neuron computations, has no doubt surprised everyone, and particularly so for those most embedded in the field.

Cataloging properties and functions of active dendrites

The rapid pace of new information about the active properties of dendrites has been largely preceded by the development of new recording and imaging techniques. In addition to methods for direct dendritic recordings mentioned above, the development and use of calcium- and voltage-sensitive indicator dyes and high-speed fluorescence imaging [29–31] led to a significant advances in our understanding of the active properties of dendrites. More recently, *in vivo* optical imaging [32,33], *in vivo* patch recordings [34] and glutamate uncaging [35] onto single spines have all added significant new details about active dendrites. The use of intracellularly loaded, voltage-sensitive dyes for monitoring the electrical activity in different parts of single neurons [36], genetically encoded fluorescence indicators for Ca^{2+}, voltage and signaling molecules, and optical activation of light-sensitive channels holds much promise for future research [37,38]. There have also been significant advances in developing specific antibodies for the immunohistochemical identification [39] and fluorescent tagging [40,41] for localization of dendritic ion channels, apart from parallel developments in the availability of better quantitative methods for visualizing dendritic structure–function relationships. Some of these include array tomography [42], optical sectioning microscopy [43], volume electron microscopy [44], stochastic optical reconstruction microscopy, STORM [45], photoactivated localization microscopy, PALM [46] and self-phase modulation [47]. There are several other exciting techniques such as optical switching of channels [48] and genetic modification of channels through viral transfection methods *in vivo* [49] that are or will be addressing important questions about the functional properties of dendrites in addition to the development and use of more and more sophisticated computational approaches [50–53].

Using some of these techniques, a great deal of effort has been spent discovering the existence, density and spatial localization of voltage-gated ion channels in dendrites. A vast majority of studies in mammals have been done on hippocampal CA1 pyramidal neurons, neocortical pyramidal neurons, cerebellar Purkinje cells and mitral cells in the olfactory bulb (in that order). The reasons for this are partly technical, because those particular neurons have large and planar dendrites making direct patch-clamp recordings feasible, but also perhaps because of the relative number of scientists studying each cell type. There are other cells and other preparations, however, that have been used for investigations of active dendrites. For example, several insects have been used to great advantage to address the actual role that active dendrites play in the behavior of the organism (reviewed in Ref. [54]). What is clear from the studies of both vertebrate and invertebrate species, however, is that the active properties of dendrites vary considerably among cell types and animal species. All neurons appear to express some types of voltage-gated ion channels in their dendrites, but the types and spatial distribution of these channels are quite diverse and determine the many different firing properties of neurons within their functioning network.

Although the mosaic for the expression pattern of voltage-gated ion channels in the dendrites of each cell type is far from understood, and for the most part has been limited to studies of the larger dendrites, there are several general principles that have emerged, at least with respect to the most studied mammalian neurons (see recent reviews [55,56]). For example, Na^+ channels appear to be uniformly expressed in the dendrites of most pyramidal neurons and mitral cells, but not in Purkinje cells or thalamocortical neurons (reviewed in Ref. [57]). The properties of the Na^+ channels in different parts of the neuron (e.g. axon, soma, dendrites), do vary, although the variations might be mostly related to different states of phosphorylation and inactivation kinetics [58–61]. The presence of dendritic Na^+ channels allows for the backpropagation of action potentials from the axon, local initiation of action potentials under some conditions [62–64] and for amplification of synaptic potentials [65–67]. The degree to which each of these signaling mechanisms occurs in different neurons is dependent on local geometry (e.g. branch diameter and branching patterns [68]) as well as the presence of other voltage-gated channels. Specific structure–function relationships between channel densities and local geometry are in general poorly understood and yet critical for the role of dendritic Na^+ channels in shaping active properties [69].

In contrast to Na^+ channels, the expression pattern of voltage-gated Ca^{2+} channels is typically very nonuniform in neuronal dendrites [56]. For example, in both CA1 and neocortical pyramidal neurons, *T*- and *R*-type channels appear to be expressed preferentially in dendrites [70–72]. *L*-type channels are expressed in soma, dendrites and possibly spines of many neurons, but at different densities [73]. Other channels such as *P*/*Q*- and *N*-type, although present in dendrites [74], are typically expressed at lower density than some of the other channel types. An exception to this, of course, is the Purkinje cell, in which *P*/*Q*-type as well as *T*-type channels are heavily expressed in dendrites [75,76]. The molecular subunits responsible for many of the Ca^{2+} channels in dendrites have yet to be determined with any certainty. The use of specific blockers can sometimes distinguish among broad classes of Ca^{2+} channels, but it is generally difficult to further identify native Ca^{2+} channels in terms of the primary and auxiliary subunits comprising the channel. For example, there are three α subunits for *T*-type channels ($Ca_v3.1$–3.3), two for *L*-type ($Ca_v1.2$ and 1.3) and one each for *P*/*Q*- ($Ca_v2.1$), *N*- ($Ca_v2.2$) and *R*-type ($Ca_v2.3$), and few of the current blockers can satisfactorily differentiate among them in native cells.

Dendritic Ca^{2+} channels are responsible (at least) for Ca^{2+} influx during synaptic events [70,77] and backpropagating action potentials [78–80] and for dendritic plateau potentials [81], which can be initiated by certain patterns

of synaptic inputs. Because intracellular Ca^{2+} is such a ubiquitous initiator for many biochemical signaling cascades, much needs to be learned about the expression pattern and dynamic regulation of dendritic Ca^{2+} channels.

K^+ channels are the most molecularly diverse type of voltage-gated ion channel in the brain [82], and K^+ channel distribution and function in dendrites are poorly understood. A dramatic example for the importance of dendritic K^+ channels comes from the finding that a gradient in channel density (increasing with distance from the soma) in the transient, *A*-type K^+ channel exists in the apical dendrites of CA1 pyramidal neurons [83] and to a lesser extent in layer 5 cortical neurons [84,85]. The expression pattern of this channel within the stratum radiatum of CA1 neurons regulates spike backpropagation, local spike initiation and synaptic potentials. By contrast, the muscarine-sensitive or *M*-type K^+ channel is expressed at a very low density in apical dendrites of these neurons [86,87], whereas delayed rectifier-type K^+ channels are more uniformly expressed [39]. There are many other broad categories of K^+ channels, such as the *D*-type [41], the Ca^{2+}-dependent BK and SK types [88–90] and inward rectifier-type K^+ channels [91] expressed in neuronal dendrites, but no general conclusions can yet be drawn about their expression patterns or function. For example, in CA1 neurons, the *D*-type was inferred from single-channel recordings to be expressed at low levels in dendrites [86], but activity can regulate local synthesis and expression, leading to dynamically regulated changes in *D*-type channels [41]. BK channels are expressed in many dendrites, but they often do not participate in Ca^{2+}-dependent hyperpolarizations [88,89]. The reasons for this are unclear, but might have something to do with subunit expression or expression levels of the Ca^{2+} channels that link to the channels [92]. SK channels are expressed in dendritic spines, are activated by Ca^{2+} influx through NMDA receptors [90] and can regulate NMDA-dependent synaptic plasticity [93]. Ca^{2+}-dependent K^+ channels that are responsible for slow after-hyperpolarizations following trains of action potentials appear to be expressed primarily in proximal dendrites [94].

Other types of voltage-gated ion channels reportedly expressed in dendrites include Na-dependent K^+ channels [95,96], voltage-dependent Cl^- channels [97] and hyperpolarization-activated (*h*) channels [98]. *h* channels in particular have received considerable attention in recent years after the demonstration by Jeff Magee [99] and later by Lörincz *et al.* [100] that they are expressed at extremely high levels in distal dendrites of CA1 pyramidal neurons, followed by a similar demonstration in cortical pyramidal neurons [101]. They also appear to be expressed in dendrites of many other neurons, although less is known about their relative distributions [57]. Their function for regulating dendritic excitability and plasticity is being pursued by many laboratories [102–105], but *h* channels have been implicated in regulating certain temporal patterns of synaptic input [106,107], neuronal oscillations [108] and subthreshold resonance properties of neurons [109]. For example, it has been demonstrated recently that the spatial gradient of *h* channel density produces a resonance frequency map in dendrites in which inputs to different regions would become differentially filtered [110].

Although this review is focused mostly on the voltage-gated ion channels that shape the active properties of dendrites, we should mention that the expression patterns for many (if not all) ligand-gated channels in dendrites are also very nonuniform. For example, NMDA- and AMPA-type glutamate receptors, different types of GABA receptors and glycine receptors have all been reported to be differentially expressed in neuronal dendrites [111–115]. Because NMDA receptors are both ligand *and* voltage dependent, they are capable of shaping the active properties of dendrites. For example, NMDA receptors in dendrites can mediate local dendritic spikes, which in turn can influence spike initiation and timing in other parts of the neuron [116,117]. They also contribute to some nonlinear electrical properties of dendrites [118,119].

Are there any general conclusions that we can draw about function from what we know so far regarding all of the voltage-gated ion channels expressed in neuronal dendrites? The answer is probably no, because of the large diversity in channel types and expression patterns among different neurons. We can, however, summarize a few frequent observations. (i) Na^+-dependent action potentials backpropagate from the axon into the dendrites of most, but not all, neurons. In many, but not all, neurons, these action potentials decrement in amplitude with distance from the soma. (ii) Na^+-dependent and NMDA receptor-dependent spikes can be initiated in dendrites of some neurons under specific sets of conditions. Oftentimes these local spikes do not propagate to the soma, or if they do, they contribute only small, sharply rising signals that can influence the timing of action potentials initiated in the axon/soma region. (iii) Dendritic Ca^{2+} channels are opened by both backpropagating action potentials and by locally initiated spikes and produce a rise in the concentration of intracellular Ca^{2+}. (iv) Dendritic Ca^{2+} channels, especially in more distal dendrites, can sustain Ca^{2+}-dependent spikes or plateau potentials. These too produce a rise in intracellular Ca^{2+}. (v) Dendritic Ca^{2+} channels can be opened by synaptic potentials and produce a rise in intracellular Ca^{2+}. (vi) Dendritic K^+ channels regulate the amplitude backpropagating action potential in some, but not all, neurons. They can also influence the site of initiation of local spikes and the amplitude of synaptic potentials. (vii) Dendritic *h* channels regulate the integration and frequency-dependent tuning of temporal patterns of synaptic input and can mediate neuronal oscillations. (viii) The different types of voltage-gated channels expressed in dendrites play important roles in how each particular neuron responds to spatial and temporal patterns of inputs [120]. Although this brief summary of the active properties of dendrites might seem complicated, the story becomes even worse (i.e. more interesting!) when we begin to consider that these active properties are not static, but dynamically regulated over wide timescales.

Plasticity of active dendrites

What do we mean by plasticity? Plasticity in general means the ability to change or deform and thereby adapt to the environment. In the realm of neuronal plasticity, a

neuron or synapse can change its features in response to a stimulus. The changes can take place on a variety of timescales, from the short term (ms) to the very long term (years). The features of a neuron or synapse that can change as a function of its prior history (or be 'plastic') are probably limited only by the number of properties of a neuron that can have some impact on its function. We will focus here only on the plasticity of the active properties of dendrites, that is, on the changes in dendritic voltage-gated ion channels due to some prior event, such as a neuromodulatory stimulus, a synaptic input or the firing of the pre- and/or postsynaptic neuron. A key property of active dendrites is their ability to participate in this plasticity of neuronal function and contribute toward mechanisms of learning and memory.

Essentially all ion channels can be phosphorylated by protein kinases and have their function altered. The properties of channels that might change accordingly include the voltage ranges and time constants of activation and inactivation, single-channel conductance and surface expression and degradation. Phosphorylation can take place in tens of milliseconds, and persist for a very long time depending on many factors (see e.g. Ref. [121]). The ability of any particular dendritic ion channel to be phosphorylated will depend on the presence of the appropriate kinases, phosphatases and signaling receptors and second messengers in the location of the dendrites where the channel is expressed.

In 1982, Steward and Levy [122] reported polyribosomes in dendrites and spines of hippocampal pyramidal neurons (see also Ref. [123]). Using microarray technology, Eberwine *et al.* [124] has identified hundreds of mRNAs in neuronal dendrites, raising the possibility of local protein translation [125,126]. Although mRNAs for some dendritically expressed channels such as Na^+ channels, Ca^{2+} channels and K^+ channels are included in that list of dendritic mRNAs, there are actually few demonstrations of locally translated voltage-gated ion channels in dendrites (see Ref. [41]). The local translation in dendrites of important signaling molecules that can modulate dendritic ion channels, however, has been well described [127]. Furthermore, activity-dependent redistribution of proteasomes, which regulate protein degradation, has recently been shown to occur in dendrites, providing another potential mechanism for plasticity of channel number and function [128].

Plasticity of dendritic ion channels [129] can be expected to affect all aspects of neuron function for which they are responsible. From a systems perspective, plasticity in dendritic ion channels should be viewed along the same lines as synaptic plasticity – as a putative mechanism that mediates learning and memory in various brain structures (see Refs [130–133]).

From the viewpoint of cellular information processing, the dominant theme that has guided the literature on plasticity of ion channels has been intrinsic excitability, or the ability of a neuron to elicit action potentials for the same synaptic inputs [132,134,135]. There are only a few reports (so far) demonstrating plasticity of ion channels directly in dendrites. These examples include second-messenger modulation of dendritic Na^+ channels [58,61], several types of K^+ channels [136–141], Ca^{2+} channels [142,143] and *h* channels [56,144,145]. Activity-dependent changes in action potential backpropagation have been reported by Tsubokawa *et al.* [146] *in vitro* and by Quirk *et al.* [147] *in vivo*. Long-term potentiation (LTP) and long-term depression (LTD) appear to be accompanied by local changes in dendritic *h* and K^+ channels [148–150] and by spatially widespread changes in dendritic *h* channels [110,151,152]. Dendritic ion channels have also been shown to be important for the induction of LTP and LTD through the regulation of backpropagating action potentials [153–157] and local spike generation [158–160].

Changes in excitability mediated by dendritic ion channels have recently been interpreted within the framework of metaplasticity [110,149], in either a location-specific or a spatially widespread manner. Metaplasticity could be broadly defined as the change in the rules governing synaptic plasticity [161]. As change in excitability of a neuron would alter the way it would respond to synaptic inputs, and hence to the way it would respond to patterns of inputs that elicit synaptic plasticity, it has been suggested that plasticity in ion channels can mediate metaplasticity [162]. This change in rules of plasticity could either offer homeostatic balance to the positive feedback nature of Hebbian synaptic plasticity [110,163] or act as a positive feedback mechanism enhancing the amount of changes a synapse can undergo [40,162]. Kim and Linden [133] recently termed these two forms of intrinsic plasticity *homeostatic* and *mnemonic*, respectively.

In the process of framing questions on intrinsic plasticity to be centered on excitability, however, the other functions of ion channels [6,164], and the role of ion-channel plasticity in modulating these functions, have been largely ignored. Prominent among these are intrinsic oscillations and intrinsic frequency response properties of neurons, which are known to be mediated by voltage-gated ion channels [6,165,166]. It has been recently shown that a resonance frequency map exists within a single neuron and can be adaptively modified as a function of postsynaptic activity [110]. Specifically, this points to the ability of a neuron not only to tune different parts of its dendrites to different frequencies but also suggests that these response properties are adaptive to the environment in which they reside. Ion channels in dendrites could thus be argued to provide additional localized control of response properties by altering their densities or properties in the dendrites.

Although there have been some studies about the synergy between intrinsic and synaptic plasticity [163,167], and on the role of intrinsic plasticity in optimal information encoding [168], the role of intrinsic plasticity in information encoding has not received much attention from theoreticians, at least as compared to Hebbian synaptic plasticity [169]. The presence of a large number of dendritic voltage-gated ion channels, and their ability to undergo local or global plasticity in response to learning tasks, makes a single neuron far more powerful as an information storage and processing unit than what would be possible from a passive tree without plasticity [51,52]. For this complex computational unit to be fully understood, it is important that dendritic ion channels and intrinsic plasticity be considered by future models in

learning theory [167] and computational neuroscience [50,53,170].

Concluding remarks

Interest in the functional properties of dendrites and how they participate in synaptic integration, synaptic plasticity, neuronal computations and disease dates back many years, with seminal contributions made by many neuroscientists along the way. It has been and continues to be a major area of research for neuroscience. Many new techniques have been developed for the investigation of dendrites, and these techniques have led to an explosion of new information. From what is currently known, it is clear that the active properties of dendrites are quite complex and their study has led to many unexpected findings such as backpropagating and local action potentials playing a role in synaptic plasticity, both the amplification and dampening of synaptic potentials, frequency-dependent tuning of spatial patterns of inputs and long-term plasticity of dendritic excitability. An even greater importance is therefore placed on gaining a better understanding of the trafficking, expression and local regulation of dendritic ion channels. The renewed interest in the field is evidenced by two recent editions of the book *Dendrites* and by an entire Gordon Research Conference devoted to dendrites. Because of their importance for excitability, synaptic integration and plasticity, this new emphasis on dendrites is both not surprising and most welcome.

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