A problem with Hebb and local spikes

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Although our understanding of the cellular properties of mammalian neurons is increasing rapidly, the computational function of their elaborate dendritic trees is still mysterious. In recent years, experiments have shown that, in pyramidal cells, individual dendritic compartments sustain local excitation spikes. These dendrites also support Hebbian synaptic plasticity, which depends on the precise temporal relationship between pre- and postsynaptic spikes. In this review we discuss what we consider to be a problem with Hebbian (i.e. spike-timing-dependent) plasticity. We argue that most of the spikes that occur in dendrites are not back-propagating action potentials but local spikes, and that Hebbian plasticity produced by local spikes can undermine the functional integrity of the geometrically complex dendritic tree. We propose that the inverted Hebbian plasticity of synapses involved in local spikes, and/or local dendritic homeostatic plasticity, could prevent an unbalanced distribution of synaptic weights on the dendritic tree.

Pyramidal neurons receive thousands of inputs onto a dendritic tree of outstanding physical complexity [1]. This geometry is characteristic of all pyramidal cells, suggesting that the pattern is of functional significance and could generate multiple, electrically and chemically isolated, compartments. Nevertheless, the exact purpose of this intricate morphology is still mysterious. Although dendrites were thought for decades to be passive cables, it is now clear that they have active conduances and intrinsic electrophysiological properties [2–5]. In pyramidal cells, electrophysiological and imaging studies have demonstrated Na⁺-based back-propagating action potentials (BAPs), which propagate quickly through large territories of the dendritic tree and trigger essentially instantaneous Ca²⁺ accumulations in spines and dendritic shafts [6,7]. In addition, local dendritic spikes, which are mediated by Na⁺ or Ca²⁺ channels or by NMDA receptors, activate restricted regions of the dendritic tree and trigger localized Ca²⁺ accumulation [8–13]. These local spikes, generated by synaptic input or glutamate uncaging, resemble those previously described in Purkinje cells [14] and are still poorly understood.

The understanding of the cellular process responsible for synaptic plasticity in pyramidal neurons is one of the central topics in current neuroscience. Following the ideas of Ariens-Kappers [15], Donald Hebb postulated that synapses participating in firing of the postsynaptic cell would become strengthened [16]. This ‘Hebbian rule’, and its corollary whereby those synapses that fail to activate their targets become weaker, has indeed been shown to occur and to explain many results – both in mature brain circuits and in the developing nervous system [17,18]. A major advancement in the understanding of Hebbian processes came about with the introduction of dual whole-cell recordings from pairs of connected neurons. In a landmark study, it was shown that long-term synaptic potentiation or depression (LTP or LTD) was precisely controlled by the arrival time of BAPs to the activated synapses [19]. If the excitatory postsynaptic potential (EPSP) occurred after the BAP arrived, LTD was produced; if the EPSP preceded or coincided with the arrival of the BAP, LTP resulted. The difference in arrival time that produced maximum LTD or LTP was extremely short (a few milliseconds). This ‘millisecond divide’ showed that Hebbian rules are implemented with exquisite precision in pyramidal cells, and demonstrated that neurons have the biophysical hardware to process precise temporal codes.

The problem with Hebb and local spikes

These results helped re-frame the Hebbian rule as spike-timing-dependent plasticity (STDP), because the key element that determines the magnitude, and even the polarity, of the synaptic plasticity is the timing of the back-propagating spike. It should be noted that a similar bimodal learning rule had already been predicted by Bienenstock et al. [20]. Since then, STDP has been observed in a variety of pyramidal cell populations in vitro [19,21–26] and also in vivo [27–29]. The exact temporal dynamics governing plasticity induction have recently been characterized at different frequencies [26] and at varying inter-spike intervals within realistic spike trains [25]. However, the universality of STDP is unclear. At the heart of STDP is the ability of the activated synapse to ‘know’ when the postsynaptic cell has generated an action potential (AP). The BAP provides this cue [21], as its arrival before or after synapse activation determines the polarity of plasticity [19]. Because the BAP is thought to be a global signal [30] it has been taken for granted that an activated synapse ‘knows’ when the cell fired.

The problem is that the BAP could represent the exception, rather than the rule, in the normal life of a synapse (which might instead experience many more frequent local spikes than global BAPs). In vivo, the prominence of BAPs is unclear. In anesthetized animals, it has been shown that BAPs are tonically suppressed and proximally restricted [31], although this is controversial in awake animals [32]. Also, the constant dendritic bombardment with EPSPs that is thought to occur in vivo [33,34] could create a dendritic environment with multiple spiking domains – which would be unlikely to possess global back-propagating properties, owing to inactivation of channels in active regions. A further complication (likely to be present continuously in the neuron) is inhibition, which can act to prevent global BAPs and to carve local spikes in dendritic space. Indeed, even in slices isolated from background synaptic activity, back-propagation into the apical dendrite can be blocked by a single inhibitory postsynaptic potential (IPSP) [35].

In addition, in in vitro experiments that have demonstrated STDP in pyramidal neurons, the postsynaptic APs were initiated non-physiologically, through the recording electrode [19,21–26]. Under these conditions, none of the dendrites actually participated in conveying...
electrical activity towards the soma to initiate the AP. This is important because previous synaptic activity can control dendritic AP propagation. First, because back-propagation depends on Na⁺ channels, and because these channels undergo an activity-dependent slow inactivation [36], strong EPSPs (suprathreshold for dendritic Na⁺ channel recruitment) can locally block AP invasion – this has been shown in neocortical [37] and hippocampal pyramidal cells [38]. Second, weaker EPSPs (subthreshold for Na⁺ channel activation) can enhance AP back-propagation by inactivating Ia K⁺ channels [39]. Because most of the experiments showing STDP in pyramidal neurons paired synaptic inputs with artificially generated postsynaptic APs, only synapses on naïve dendrites have been examined. Thus, in these studies, the back-propagating AP was unrealistically global.

Therefore, if STDP were applied to synapses that participate in local spike generation, a positive feedback loop would ensue. By this, potentiated synapses would trigger local spikes more often and, thus, lead to their further potentiation. Because of the prevalence of local spikes, use of purely Hebbian rules would cause pyramidal cells to face the problem of creating dendritic compartments that would become functionally dominant at the expense of others (Fig. 1).

**One solution: local dendritic spikes and inverted Hebbian rules**

It seems to us that neurons must normalize the excitability of individual dendritic compartments. At least two mechanisms could operate. First, in the background of STDP driven by BAPs, local spikes could produce learning rules of opposite polarity to STDP. Strongly activated, spiking dendritic domains produce distinct, longer Ca²⁺ transients [12,13], which can initiate distinct signaling pathways. If synapses driving local dendritic spikes were weakened, the net effect of STDP would be to distribute synaptic weights spatially. Indeed, the pairing of glutamate uncaging over restricted CA1 pyramidal-cell dendritic domains with postsynaptic depolarization resulted in LTD [40,41]. This was surprising, as similar protocols using synaptic stimulation at the same synapses were known to cause LTP [42,43]. It is possible that local spikes were produced in the caged-glutamate experiments, as reported in similar studies [12,13]. Nevertheless, uncaged glutamate stimulates receptors in a different spatio-temporal manner than would synaptic glutamate, so it is possible that the LTD resulted from stimulated extrasynaptic receptors, whose concentration or kinetics could differ from synaptic ones.

**Another solution: local homeostatic plasticity**

Another solution to this global STDP problem could be homeostatic plasticity at the local dendritic level. In neuronal cultures, two related forms of homeostatic plasticity have been discovered that average activity over long time scales (hours to days) and that might act in vivo to stabilize net excitability. First, activity blockade resulted in a time-dependent increase in the amplitude of spontaneous AMPA miniature excitationatory postsynaptic currents (mEPSCs), and hyperactivity had the opposite effect [44]. These slowly evolving change in synapse strength (synaptic scaling) were distinct from Hebbian plasticity, not only in their reversed polarities, but also in their time course and mechanisms. Pre- and postsynaptic temporal correlations were not necessary and NMDA-receptor blockade had no effect, yet brain-derived neurotrophic factor (BDNF) and an as-yet-uncharacterized depolarization-activated signal could regulate the change [45,46]. In addition to this synaptic scaling, hypo-activity in cultured neurons caused compensatory changes in neuronal intrinsic excitability [47]. Action potential threshold decreased and frequency–current curves grew steeper, owing to the combined effects of increased Na⁺- and decreased K⁺-channel densities. These changes increase the gain of synaptic input, such that a given synaptic current could both initiate spiking more easily and generate more spikes.

Although all of the activity manipulations in these experiments were global in nature, it is likely that these mechanisms can also act on a local dendritic level. BDNF can act extremely locally (with a range of 30 µm) [48] and its effect is dose-dependent, suggesting that neurons could be sensitive to BDNF gradients. Thus, it is reasonable to imagine that AMPA currents could be scaled up at
activity-starved dendritic compartments and that AMPA currents could be scaled down at dendrites that are chronically depolarized by repeatedly active, convergent afferents. Local control of Na⁺- and K⁺-channel densities could regulate the threshold for local spike generation.

Summary

The problem of how pyramidal neurons regulate the topographical distribution of input strengths—how they prevent specific dendritic compartments from becoming too dominant or others from becoming too silent—could be solved by local implementation of homeostatic plasticity, local spikes with inverted learning rules using local spikes (instead of BAPs) contributing to the topographical regulation of plasticity, local spikes with inverted learning rules, or both. Local spikes might contribute to the topographical regulation of inputs, and the question of how STDP rules using local spikes (instead of BAPs) remains open. Finally, current work on homeostatic processes emerges from their local operation.

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