Postsynaptic depolarization requirements for LTP and LTD: a critique of spike timing-dependent plasticity

John Lisman & Nelson Spruston

Long-term potentiation and long-term depression require postsynaptic depolarization, which many current models attribute to backpropagating action potentials. New experimental work suggests, however, that other mechanisms can lead to dendritic depolarization, and that backpropagating action potentials may be neither necessary nor sufficient for synaptic plasticity *in vivo*.

In Hebb's seminal proposal, a synapse becomes stronger if the presynaptic cell is active and if the resulting excitatory postsynaptic potential (EPSP) contributes to the firing of an action potential in the postsynaptic cell. Hebb's idea has been strengthened by the finding that many synapses undergo long-term potentiation (LTP) and that this process requires both presynaptic activity and strong postsynaptic depolarization. Furthermore, the NMDA class of glutamate receptors is critically involved in this process. To open, these channels require both glutamate and postsynaptic depolarization; the resulting Ca^{2+} entry then activates the biochemistry of potentiation. Despite the long-standing recognition of the importance of postsynaptic depolarization for synaptic plasticity, it is only recently that data are becoming available about the nature of the critical depolarizing events within the dendrites themselves (for reviews, see refs. 1–3).

The discovery that fast (1–2 ms), Na^+-mediated action potentials are initiated in the axon and propagate into the dendrites of hippocampal and cortical pyramidal cells (reviewed in refs. 4,5) raised the possibility that such depolarizing events, termed backpropagating action potentials (bAPs), might be the critical postsynaptic depolarization responsible for Hebbian plasticity. Support for this idea was provided by experiments on cortical pyramidal neurons[6]. In these experiments, a small unitary EPSP was evoked by stimulating a single presynaptic cell, and a single bAP was induced by brief current injection into the soma of the postsynaptic cell. Directly evoking the action potential gives the experimenter control over the timing of the action potential relative to the EPSP. When the bAP occurred near the beginning of the EPSP, this resulted in LTP (provided this protocol was repeated many times), suggesting a critical role for the bAP in LTP. Furthermore, it was found that the timing of the bAP affected the sign of the synaptic modification; if the spike occurred in a small window (<40 ms) just before the EPSP, long-term depression (LTD) was induced. This timing dependence has now been observed in several types of cortical[6–8] and hippocampal neurons[9,10]. More complex rules have been elucidated to explain plasticity that occurs during more complex spiking patterns[11,12].

These findings have led to a widely accepted theory of spike timing–dependent plasticity (STDP). In its standard form, the theory is as follows: the timing of the bAP relative to the EPSP determines the sign and magnitude of synaptic modification. This rule has been incorporated into numerous computational models (about 50 by recent estimate). Here we argue that this theory does not capture important aspects of the conditions leading to LTD and LTP. Specifically, the data to be reviewed here indicate that the bAP is neither necessary nor sufficient for LTP. Thus, although the bAP is certainly an important neural signal and can influence plasticity, it is unlikely that the bAP by itself is the critical postsynaptic depolarization that controls bidirectional plasticity.

The bAP is not sufficient for LTP

What complicates the interpretation of standard STDP experiments is that many EPSP-spike pairings are required to induce synaptic modifications. Moreover, in most studies, there is a specific range of repetition rates that must be used for successful induction: at frequencies below 10 Hz, LTP cannot be induced[6,8]. This repetition rate requirement suggests that something more than simply a pairing of EPSPs and bAPs is necessary for the induction of LTP. Indeed, the repetition rate requirement is puzzling because the ability of bAPs to invade the dendrites is decreased as their frequency is increased[13–16].

Recent work gives insight into the repetition rate requirement and directly demonstrates that the bAP alone is not sufficient for LTP induction: rather, an additional depolarization is required[8]. In principle, the repetition rate requirement could be due to electrical and/or short-term biochemical integration. Sjostrom *et al.*[8] provided direct evidence for the importance of electrical integration; they observed a buildup of voltage as a result of repetitive stimulation at 10 Hz or higher. They found that if this buildup was mimicked by positive current injection, LTP could be induced at low frequency, whereas if the buildup was inhibited by brief pulses of negative current, LTP could not be induced, even at 40 Hz. Thus, it

John Lisman is at the Volen Center for Complex Systems, Biology Department, Brandeis University, 415 South Street, Waltham, Massachusetts 02454, USA, and Nelson Spruston is at the Institute for Neuroscience, Department of Neurobiology & Physiology, Northwestern University, 2205 Tech Dr., Evanston, Illinois 60208, USA.
e-mail: Lisman@brandeis.edu

seems that the repetition rate requirement for LTP induction can be understood in terms of the temporal integration required to achieve a critical depolarization that must occur in addition to the bAP. This critical depolarization can also be met by increasing the number of synaptic inputs (in the slice preparation)[7,8] or by using cultured cell preparations where the number of synapses in a unitary connection is higher than in the slice[9,10]. When spatial summation of this kind occurs (termed cooperativity), temporal summation is no longer required, and LTP can be induced with low-frequency repetition.

One reason the bAP may not provide sufficient depolarization is because of its brief duration. Although single bAPs invade the dendrites and influence NMDA channels[17,18] they may be insufficient to relieve the Mg^{2+} block of NMDA receptors in a way that leads to LTP. This is likely to be due to the fact that bAPs are brief (1–2 ms), and relief of Mg^{2+} block at NMDA receptors is not instantaneous[19–22]. Thus, the need for additional depolarization to induce LTP may arise from the need for a longer depolarization in order to effectively relieve Mg^{2+} block of NMDA receptors and thereby adequately activate the Ca^{2+}-dependent biochemical processes that enhance transmission.

What exactly is this additional depolarization? The available recordings of voltage changes during LTP induction in cortex have been made from the soma. Because of electronic attenuation, such recordings are not very informative about the magnitude and occurrence of dendritic potentials (such as dendritic spikes). Thus, there are several scenarios that need to be considered. The simplest is that the required temporal and/or spatial integration makes the EPSP itself large enough to activate NMDA channels. Dendritic recordings during successful LTP induction in hippocampal neurons[23] show that an EPSP that is only modestly above threshold in the soma is much larger in the dendrites. Indeed, the dendritic EPSP can reach –30 mV, a voltage where NMDA-mediated Ca^{2+} influx is maximal[24]. In a second scenario, the additional depolarization enhances the backpropagation of the spike, perhaps increasing its amplitude or duration at the synapse[25,26]. In a third scenario, the depolarizing effects of the bAP and the integrated EPSP bring the dendritic voltage to the threshold for a dendritic spike (other than the bAP), the occurrence of which is required for LTP induction. It has long been known that dendrites contain a variety of voltage-dependent Ca^{2+} and Na^{+} channels that can give rise to dendritic spikes (reviewed in ref. 27), and recent work shows that NMDA channels can also generate dendritic spikes[28]. Several studies on hippocampal pyramidal cells[23,29,30] have shown that dendritic spikes can occur during LTP induction and that there is a correlation between the occurrence of such spikes and successful LTP induction. (Note that these papers did not use spike timing protocols.) Further experiments will be needed to distinguish among these scenarios. In any case, it is clear is that the bAP by itself does not provide sufficient depolarization to trigger STDP.

bAPs are not required for LTP or LTD

Recent experiments have provided the first test of whether bAPs are necessary for LTP under physiological conditions. In most STDP experiments, the EPSP is subthreshold, and the bAP is triggered non-physiologically by current injection into the postsynaptic cell. If these spikes are not evoked or not allowed to backpropagate, plasticity does not occur[6,23,26]. But what would happen in the more physiological condition in which the bAP is caused by a suprathreshold EPSP rather than by current injection? Golding and colleagues showed that strong synaptic stimulation was able to induce LTP even when bAPs were blocked by application of tetrodotoxin (TTX) near the soma. This was true not only for distal synapses (perforant path), where bAPs are very small, but also for more proximal synapses (Schaffer collaterals), where bAPs are larger[23]. Thus, it seems that bAPs are not required for LTP when action potentials are evoked by synaptic stimulation rather than current injection through an electrode. In these recordings, dendritic spikes were evident, raising the possibility that such spikes, rather than the bAP, are critical for LTP induction.

Large EPSPs and dendritic spikes have been observed *in vivo*[31], suggesting that the conditions necessary to induce LTP without bAPs are likely to be physiologically relevant. Furthermore, recent work[32] has demonstrated that dendritic spikes may occur in small-diameter branches of both the basal and apical branches, even during stimuli considerably weaker than those used by Golding and colleagues[23]. Nevertheless, these results do not exclude the possibility that under different conditions, the bAP would be required. For instance, one might imagine that if synaptic input into basal dendrites were used to produce bAPs, they would propagate into the apical dendrites and induce LTP. Conversely, action potentials induced by strong stimulation of the apical dendrites could propagate into basal dendrites and contribute to the potentiation of weak synapses activated in this region. Thus, if properly timed, LTP would be induced, just as during standard STDP protocols. However, even here there may be unexpected problems; as inhibitory interneurons project across cortical layers[33], interneuron activity evoked by repetitive stimulation in the basal region could impinge on apical dendrites[34,35] and block the bAP[36,37]. The only way to find out whether STDP protocols can induce LTP under natural conditions (that is, without artificial sources of depolarization) will be to test this directly. Such experiments are important, because they will provide crucial information regarding the spatial relationships that can successfully lead to associative LTP. At least some spatial pairings are not likely to work. For example, strong activation of basal dendrites would not be likely to lead to potentiation of weaker synapses in distal dendrites that are beyond the reach of the bAP.

The role of the bAP in the induction of LTD is also unclear. Recent evidence suggests that suppression of NMDA receptors by spike-mediated calcium entry may be a necessary step in the induction of LTD[38]. Thus, it is possible—perhaps even likely—that the bAP may be important for spike timing–dependent LTD, but this has never been tested directly. Certainly there is ample evidence that the bAP is not required for LTD, as other forms of LTD can be induced without postsynaptic action potentials[39–42]. Furthermore, other sources of depolarization may also contribute to calcium entry before NMDA receptor activation. For instance, the synaptic depolarization that normally triggers an action potential may also result in dendritic spikes that contribute to LTD[42].

In summarizing these results, we emphasize that the findings of STDP are not in question; the experiments have been well done and have been replicated. Rather, what is at issue are two points: first, in almost all published experiments (which use small EPSPs), the action potential is artificially provided and is indeed necessary for LTP and LTD under these conditions. However, because of temporal and/or spatial integration, additional voltage changes occur, and these are also required for LTP induction; the bAP is not sufficient. Second, under the more physiological conditions in which the bAP is triggered by synaptic input rather than current injection, the only study conducted thus far indicates that the bAP is not required for LTP. Therefore, further work will be required to determine whether there are physiological conditions where the bAP is required for STDP.

The need for a realistic model of LTP/LTD

A computationally useful property of STDP is that small differences in the timing of pre- and postsynaptic activity can determine whether synapses are strengthened or weakened (reviewed in ref. 43). It remains possible that a variant of this timing rule will turn out to be valid even when the full complexity of dendritic events is taken

into consideration. For instance, recent evidence indicates that the repetition rate requirement is circumvented, and LTP can be induced at low repetition rates, if bursts (instead of single action potentials) are paired with EPSPs in layer 2/3 cortical neurons (T. Nevian & B. Sakmann, *Soc. Neurosci. Abstr.* 58.12, 2004), which is consistent with results obtained in hippocampal neurons[29,44]. It is also possible, however, that some factor other than EPSP/spike timing will turn out to be critical. Factors that have the demonstrated ability to control the magnitude and sign of plasticity include the level of postsynaptic depolarization[45], the rate of synaptic inputs[46] and the phase of synaptic input relative to ongoing theta frequency network oscillations[47–49] or gamma frequency oscillations[50]. Establishing which of these factors are most relevant to brain function will require *in vivo* analysis.

Elucidating the requirements for plasticity will provide insight into how easily information stored at synapses can be disrupted. At one extreme is the view to emerge from the theoretical community based on the simplest model of STDP (in most published models, the repetition rate requirement is not included). According to this view, each time an EPSP and spike occur within a temporal window, LTP or LTD may occur. As EPSPs and action potentials are common, there is little barrier to synaptic modification, and stored information becomes vulnerable to erasure[51]. At the other extreme is the possibility that the requirements for synaptic modification may be much higher and may be protected by multiple thresholds that have to be crossed before weights can be persistently modified. Indeed, there is evidence for at least three thresholds. First, a critical dendritic depolarization may have to be reached as a result of temporal or spatial integration of EPSPs and bAPs (see above). Second, repetition over many pairings may be required to trigger a biochemical integrator that underlies the nonlinear induction of LTP[52]. For instance, the CaMKII activation required for LTP induction[53] depends on cumulative autophosphorylation in a highly cooperative way[54,55]. Finally, entry of LTP into a persistent 'late phase' requires additional neuromodulatory signals influenced by systems-level evaluation of the importance of the information[56,57]. Because of these thresholds, the effect of single EPSP-spike pairings is likely to be minimal, allowing a regime in which synaptically stored information can be accessed without necessarily modifying it. Incorporating these thresholds into theoretical models would be a useful advance.

In closing, it is appropriate to come back to Hebb's rule. We do not yet know the nature of the postsynaptic depolarization that underlies Hebbian plasticity. If the bAP is not the uniquely critical determinant, what other sources of depolarization are essential? In the past, technical limitations made it difficult to study events in the dendrites with biophysical rigor. Fortunately, new electrical and optical methods (such as dendritic patch-clamp recording, two-photon imaging and voltage-sensitive dyes) are now available and can be applied both *in vitro* and *in vivo*, making this an exciting and tractable problem.

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