



INTRODUCTION BY CHIEF EDITOR MARY B. KENNEDY

The Editors of the Special Issue on “Spike-Timing Dependent Plasticity,” Jesper Sjöström and Henry Markram, asked John Lisman and Nelson Spruston to summarize and elaborate on their 2005 commentary (Lisman, J., and Spruston, N. (2005). Postsynaptic depolarization requirements for LTP and LTD: a critique of spike timing-dependent plasticity. *Nat Neurosci* 8, 839–841) in light of more recent research. Their manuscript sparked a good deal of discussion in the interactive review forum. Lisman and Spruston responded to the many issues and questions raised by reviewers and the result is a useful and informative exposition of their reservations about the concept of Spike-Timing Dependent Synaptic Plasticity (STDP). Jesper Sjöström agreed to write a reply supporting the utility of the concept. We think the two points of view, not entirely mutually exclusive, provide a healthy debate for the field and we hope readers enjoy it!

Questions about STDP as a general model of synaptic plasticity

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According to spike-timing-dependent plasticity (STDP), the timing of the Na⁺ spike relative to the EPSP determines whether LTP or LTD will occur. Here, we review our reservations about STDP. Most investigations of this process have been done under conditions in which the spike is evoked by postsynaptic current injection. Under more realistic conditions, in which the spike is evoked by the EPSP, the results do not generally support STDP. For instance, low-frequency stimulation of a group of synapses can cause LTD, not the LTP predicted by the pre-before-post sequence in STDP; this is true regardless of whether or not the EPSP is large enough to produce a Na⁺ spike. With stronger or more frequent stimulation, LTP can be induced by the same pre-before-post timing, but in this case block of Na⁺ spikes does not necessarily prevent LTP induction. Thus, Na⁺ spikes may facilitate LTP and/or LTD under some conditions, but they are not necessary, a finding consistent with their small size relative to the EPSP in many parts of pyramidal cell dendrites. The nature of the dendritic depolarizing events that control bidirectional plasticity is of central importance to understanding neural function. There are several candidates, including backpropagating action potentials, but also dendritic Ca²⁺ spikes, the AMPA receptor-mediated EPSP, and NMDA receptor-mediated EPSPs or spikes. These often appear to be more important than the Na⁺ spike in providing the depolarization necessary for plasticity. We thus feel that it is premature to accept STDP-like processes as the major determinant of LTP/LTD.

Keywords: Ca spike, Na spike, NMDA, LTP, LTD

It is well established that depolarization of the postsynaptic neuron can promote LTP by allowing the activation of NMDA receptors. Furthermore, smaller depolarizations may be necessary for the induction of LTD. Given this role of postsynaptic voltage in plasticity, it is important to establish how such depolarization is generated. According to the literal interpretation of Hebb's postulate, postsynaptic action potentials produce the required depolarization. This idea has been made plausible by the finding (Stuart and Sakmann, 1994) that action potentials backpropagate from the soma into the dendrite and can thus affect the synapses there.

The field of STDP developed after the observation that the timing of backpropagating Na⁺ spikes relative to the EPSP can determine the sign of synaptic plasticity (reviewed in Caporale and Dan, 2008). It is thus now widely assumed that such spikes are critical in

the synaptic plasticity process; indeed, this assumption is the basis of numerous theoretical models. However, there are serious reasons to doubt whether spike timing is a major determinant of synaptic plasticity. Almost all experiments demonstrating STDP have been done under conditions in which the experimenter induces the postsynaptic spike by current injection. If STDP is an important phenomenon, it must also apply when the spike is evoked naturally by the EPSP. In a previous review, we presented a critique of STDP, questioning whether it occurs under such natural conditions (Lisman and Spruston, 2005). We thank the editors of this volume for inviting us to summarize this critique here. In the interest of brevity, we express our concerns about STDP in a series of short questions/answers. Readers wanting additional information should consult our previous review.

1. Question: *Is a Na⁺ spike necessary for synaptically induced LTP?* Answer: *Eliminating the spike often has no effect* (Golding et al., 2002; Remy and Spruston, 2007; Hardie and Spruston, 2009).
2. Question: *Does the lack of a requirement for the Na⁺ spike make sense?* Answer: *Yes, because dendritic recordings show that back-propagating action potentials are always brief and often small (especially in distal dendrites) compared to other forms of dendritic depolarization* (Stuart et al., 1997).
3. Question: *Are Na⁺ spikes necessary for synaptically induced LTD?* Answer: *Not in general. LTD can be induced following low-frequency stimulation with or without spikes* (Dudek and Bear, 1992; Sjöström et al., 2001; Staubli and Ji, 1996; Wittenberg and Wang, 2006). Na⁺ spikes tend to enhance LTD, despite the fact that according to STDP the pre-before-post timing predicts LTP.
4. Question: *Perhaps the spike is unimportant during synaptically induced LTP/LTD, but doesn't the spike do the job in STDP protocols (when the spike is induced by current injection)?* Answer: *The repetition rates typically used are so high that other types of dendritic events such as Ca²⁺ spikes may be inadvertently induced by summation of EPSPs, complicating the interpretation. If lower repetition rates are used, single spikes no longer induce LTP/LTD unless larger EPSPs are used, suggesting the importance of additional sources of depolarization* (Sjöström et al., 2001).
5. Question: *Theoretical work has shown that the causal role of the presynaptic spike in generating the EPSP, which then generates the postsynaptic spike, is an elegant principle; should this concept be revised?* Answer: *Yes, there are cases in which the EPSP evokes a spike, but the result is LTD, not LTP (see question 3) and there are cases when the spike is not necessary for LTP (see question 1). Thus, spike timing is probably not the best approach to modeling synaptic plasticity (see below).*
6. Question: *Theoretical work has shown that the timing relation of presynaptic and postsynaptic events can produce important computations; should this be given up?* Answer: *No. Timing will inevitably be important because of the properties of the NMDA receptor (depolarization before glutamate binding doesn't open the channel, whereas the reverse order does). When we learn what the critical depolarizing event is (or are), timing will certainly be important.*
7. Question: *If the backpropagating spike is not the critical factor for synaptic plasticity, what is?* Answer: *The AMPA-mediated EPSP, NMDA receptor-mediated plateau potentials, and dendritically initiated Ca²⁺ spikes are plausible candidates* (Gordon et al., 2006; Kampa et al., 2007).
8. Question: *Isn't STDP elegant because of its computational consequences?* Answer: *No, it isn't as elegant as it may seem because information can't be read out (by EPSP-evoked spikes) without modifying stored information. If there is a higher threshold for plasticity (e.g., bursts or calcium spikes), it becomes possible to read out information using single spikes without modifying stored information.*
9. Question: *How is the critical source of the postsynaptic depolarization required for plasticity going to be determined?* Answer: *It's a hard problem. Some of the most advanced methods (paired recording and glutamate uncaging) will not suffice because they don't stimulate inhibition. Given the likely role of voltage-dependent conductances (including NMDA receptors), the occurrence and duration of depolarizing events will depend strongly on inhibition, which must therefore be part of the overall story* (Davies et al., 1991; Remondes and Schuman, 2002).

We are encouraged by a recent model that explains a wide range of experimental observations using an approach that does not focus on the backpropagating action potential as the sole source of dendritic depolarization (Clopath et al., 2010). Using a combination of factors related to the pre and postsynaptic membrane potentials (see also Spruston and Cang, 2010), the model explains the dependence of LTP/LTD on stimulus frequency, postsynaptic bursting, and the synaptic depolarization. Future implementations of the model could seek to explain the dependence of synaptic plasticity on specific biophysical events, such as dendritic spikes and inhibition, in compartmental models of neurons with elaborate dendritic trees endowed with a variety of conductances. It will also be of interest to see whether this class of model can also explain why the phase of synaptic stimulation during theta frequency oscillations can determine whether LTP or LTD is induced (Huerta and Lisman, 1995; Hyman et al., 2003; Kwag and Paulsen, 2009).

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LISMAN AND SPRUSTON RESPONSE TO REVIEWERS

We thank the reviewers for their comments, most of which were understanding of our skeptical position. However, several reviewers strongly disagreed with us. We suggest that these disagreements have to do with the definition of STDP. In the widely used Neuroscience text by Purves et al. (2008), an entire page is devoted to STDP. A simple definition is given: LTD is triggered when the postsynaptic spike occurs in a time window before the presynaptic spike and LTP is triggered by a postsynaptic spike that occurs in a time window after the presynaptic spike. It is stated that the spike provides the depolarization that allows Ca^{2+} entry through the NMDA channel to trigger synaptic plasticity.

All science involves simplifications. We feel that STDP, as defined above, constitutes a dangerous oversimplification. Many theoretical papers have utilized the form of STDP defined above to understand how synaptic plasticity explains brain function. The conclusions of these papers must be regarded with skepticism because the simplified view of plasticity incorporated into this definition of STDP is quite far from the truth. It ignores the fact that both LTP and LTD can occur without postsynaptic spikes and that spikes that obey the pre–post timing rule – predicted to result in LTP – can produce LTD instead (in the hippocampus). Finally, spikes don't even reach many synapses, whereas other processes strongly depolarize those synapses. None of these observations are taken into consideration by the textbook definition of STDP. One reviewer believed that we don't think that spikes and timing are important in plasticity. To the contrary, we believe they are a part of the story, along with many other factors. So far, no simple formulation has resulted that would provide non-experts or theorists with a clear understanding of the voltage processes that determine whether LTP or LTD will occur. This is not embarrassing; there are many other memory processes that are not well understood. The neuroscience community needs to understand that synaptic plasticity is still not well understood and that the elegant rules of STDP do not capture enough of the truth to be applied as a general model of synaptic plasticity in naturally active neural circuits.

Several reviewers made good points about our concern that experimentally induced postsynaptic spikes might not be sufficient to induce plasticity. One of our concerns was that the backpropagating action potentials, at high frequency or in combination with synaptic input, could trigger a Ca^{2+} spike (Larkum et al., 1999) and that this Ca^{2+} spike is what is critical for LTP induction (Kampa

et al., 2006). One reviewer made the valid point that the biophysical mechanism does not matter for the essential concept: thus even if the backpropagating Na^+ spike works by triggering another type of electrical event, it still remains true that the Na^+ spike has a causal role.

For STDP to be considered valid *in vivo*, it must at a minimum be demonstrated to occur in experiments where the spike occurs realistically (i.e., by the action of the EPSP) rather than by injection of current into the postsynaptic cell. We referred to experiments showing that spikes evoked by the EPSP are not necessary for LTP, contrary to STDP. Three reviewers objected to this challenge to STDP. One objected, citing Magee and Johnston (1997). However, that paper is not relevant because spikes were induced by somatic current injection rather than synaptically. Another rightly pointed to a paper that used low repetition rates (0.3 Hz) to induce LTP (Campanac and Debanne, 2008). However, the factors that cause very similar protocols to induce LTD in other studies (Wittenberg and Wang, 2006) need to be identified. Finally, a reviewer claimed that Zhang et al. (1998) proved the importance of spikes produced by the EPSP. This paper is indeed one of the few papers that measured spikes evoked by the EPSP (in tectal cells of *Xenopus*). The authors posed the critical question of whether spikes are necessary for LTP. To investigate this, they gave synaptic stimulation while voltage clamping the cell to -70 mV and found that LTP could not be induced. However, because all forms of synaptically induced depolarization (AMPA-mediated EPSPs, Ca^{2+} spikes, NMDA spikes) will be reduced under voltage-clamp, this experiment cannot be used to demonstrate the specific role of the Na^+ spike. It is quite possible that when more experiments are done, it will turn out that Na^+ spikes are indeed critical in these cells (contrary to what was found in the hippocampus). However, a field must not go beyond the data. The existing data argues only that Na^+ spikes can influence various forms of LTP and LTD; simple rules regarding the timing of presynaptic and postsynaptic spikes do not explain enough of the experimental data to be regarded as a good model of plasticity in naturally active neural circuits. Thus, the textbook definition of STDP should be viewed with skepticism and more robust models of synaptic plasticity should be pursued. One review article referred to this notion as “beyond classical STDP” (Kampa et al., 2007). We agree that we need to move beyond classical STDP, but wonder if a different moniker will better represent the dependence of LTP and LTD on factors other than just timing.

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Of mice and men: why investigate timing in plasticity?

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*But little Mouse, you are not alone,
In proving foresight may be vain:
The best laid schemes of mice and men
Go often askew,
And leave us nothing but grief and pain,
For promised joy!*

Robert Burns, 1785

In their critique of STDP, Lisman and Spruston highlight several points regarding STDP that they feel are problematic. The majority of these points center around the postsynaptic Na⁺ spike and its role in synaptic plasticity. They argue that the postsynaptic Na⁺ spike is not necessary in plasticity, which might seem to reduce the importance and generality of the STDP concept. For example, they point out that you can induce LTP in the hippocampus without somatic Na⁺ spikes; dendritic spikes are sufficient (Golding et al., 2002). Also, when Na⁺ spikes are “evoked naturally” via incoming EPSPs, LTD instead of LTP is induced (Wittenberg and Wang, 2006), even though your typical STDP experimental paradigm would result in LTP under similar conditions (cf. Magee and Johnston, 1997). Lisman and Spruston also argue that the standard textbook definition of STDP is unclear, which in all fairness it probably is.

It is tempting to debate each individual point, because for each paper supporting a point (e.g., Wittenberg and Wang, 2006), one can find another in disagreement (e.g., Campanac and Debanne, 2008). This, however, would not seem interesting or worthwhile. Besides, Lisman and Spruston do highlight in their critique some general and bigger-picture shortcomings in the STDP field that need to be addressed. For example, the focus on the role of the somatic action potential in STDP could mean that researchers are heading down the wrong path, since plasticity can also depend on the timing of local dendritic spikes (cf. Froemke et al., 2010b). Also, the existence of classical STDP can be questioned on experimental grounds, at least in the hippocampus (Buchanan and Mellor, 2010). Finally, STDP might be secondary or perhaps even epiphenomenal to other, more fundamental learning rules (Shouval et al., 2010).

So, instead of belaboring the details of the postsynaptic Na⁺ spikes and its role in plasticity (which I have belabored elsewhere, cf. Sjöström et al., 2008), I wish to emphasize the striking and ubiquitous timing dependence of synaptic plasticity that has been borne out of the STDP experimental paradigm. Indeed, changes in

temporal differences as small as a millisecond can switch the sign of plasticity from LTD to LTP or vice versa (Froemke et al., 2010a). Intriguingly, this acute sensitivity of plasticity to temporal order appears to exist across species as diverse as *Xenopus laevis* (Richards et al., 2010; Tsui et al., 2010), rodents (Froemke et al., 2010a), and humans (Müller-Dahlhaus et al., 2010; Silva et al., 2010). This preservation of STDP across the 340 millions years of evolution that have passed since the mammalian amniote ancestors diverged from the amphibian reptiliomorph counterparts would seem to support the idea that it is important.

And yet, even though the phenomenology of this acute timing-dependence in plasticity has been preserved, the mechanisms that underlie it can vary tremendously at different synapse types in the same mammalian brain. Seemingly identical forms of timing-dependent LTD, for example, rely on presynaptic NMDA receptors at some central synapse types but not at others (Rodriguez-Moreno et al., 2010). Could STDP have been invented by nature several times, through convergent evolution? Finally, the timing requirements of plasticity are often cell specific, with different cell types of the same brain region exhibiting specialized forms of STDP (Fino and Venance, 2010), of which inhibitory cells are a particularly striking case (Lamsa et al., 2010).

To conclude, since STDP exists – in many forms and at many synapse types, remarkably well preserved in its classical form in species as diverse as mice and men – we scientists are compelled to investigate it. We are driven to ask: why are these temporally sensitive learning rules so ubiquitous in the central nervous system, why so diverse, yet so specific, and why *so preserved*? Although evoking the postsynaptic Na⁺ spike via direct current injection may be less than entirely natural, it seems to me a reasonable starting point and an experimental scheme as good as any for the investigation of temporal sensitivity. Nevertheless, as Robert Burns observed over 200 years ago, proving foresight may be vain, and the best laid schemes go often askew. We thus need to keep in mind that our present interpretations may be overly influenced by fleeting fads and ephemeral fashions in science, and may well turn out to be only partially correct or even entirely erroneous in the future. Ultimately, this is what Lisman and Spruston’s critique should remind us of (Lisman and Spruston, 2005), and herein lies its strength. Indeed, maybe STDP as a model of plasticity can be improved upon?

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