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Mechanisms and significance of spike-timing dependent plasticity

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Abstract. Hebb's original postulate left two important issues unaddressed: (i) what is the effective time window between pre- and postsynaptic activity that will result in potentiation? and (ii) what is the learning rule that underlies decreases in synaptic strength? While research over the past 2 decades has addressed these questions, several studies within the past 5 years have shown that synapses undergo long-term depression (LTD) or long-term potentiation (LTP) depending on the order of activity in the pre- and postsynaptic cells. This process has been referred to as spike-timing dependent plasticity (STDP). Here we discuss the experimental data on STDP, and develop models of the mechanisms that may underlie it. Specifically, we examine whether the standard model of LTP and LTD in which high and low levels of Ca^{2+} produce LTP and LTD, respectively, can also account for STDP. We conclude that the standard model can account for a type of STDP in which, counterintuitively, LTD will be observed at some intervals in which the presynaptic cell fires before the postsynaptic cell. This form of STDP will also be sensitive to parameters such as the presence of an afterdepolarization following an action potential. Indeed, the sensitivity of this type of STDP to experimental parameters suggests that it may not play an important physiological role in vivo. We suggest that more robust forms of STDP, which do not exhibit LTD at pre–before–post intervals, are not accounted for by the standard model, and are likely to rely on a second coincidence detector in addition to the NMDA receptor.

1 Introduction

The notion that when a pre- and a postsynaptic neuron undergo coincident activation the synaptic strength between them increases is conceptually appealing. It provides a mechanism for the formation of associations and classical conditioning, as well as the formation of self-organizing maps. For example, William James' laws of mental associations (James 1890, p. 561):

> ... objects once experienced together tend to become associated in the imagination, so that when any one of them is thought of, the others are likely to be thought of also, in the same order of sequence or coexistence as before. This statement we may name the law of mental association by contiguity.

is elegantly addressed at the neural level by Hebb's postulate (Hebb 1949):

> When an axion [sic] of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

There are two questions that are not addressed by Hebb's presentation of his hypothesis. He did not speculate as to the effective time windows between pre- and postsynaptic activity that would lead to potentiation. In addition, while he suggested the conditions under which synapses may undergo an increase in synaptic strength, he did not specify the conditions that would cause a decrease.

1.1 Associative long-term potentiation

Although Hebb's postulate was made in 1949, and long-term potentiation (LTP) of synapses was described in 1973 (Bliss and Lomo), it was not until 1986 that Hebbian associative synaptic plasticity, or associative LTP, was convincingly demonstrated (Kelso et al. 1986; Malinow and Miller 1986; Sastry et al. 1986; Wigström et al. 1986). Two facts were of primary importance in establishing the existence of associative LTP: (i) it could be achieved by pairing single presynaptic events with intracellularly produced postsynaptic depolarization, and (ii) it was shown to be pathway specific; that is, if an independent second presynaptic pathway was

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activated in an unpaired manner it did not undergo potentiation.

1.2 Spike-timing dependent plasticity

An important extension of Hebbian or associative synaptic plasticity was brought to light by experimental data showing that not only did the temporal relationship between pre- and postsynaptic activity determine whether or not LTP was induced (Gustafsson et al. 1987), but also that it could determine the direction of plasticity in synapses from several brain areas (Levy and Steward 1983; Debanne et al. 1994, 1998; Markram et al. 1997; Bi Poo 1998; Zhang et al. 1998; Feldman 2000; Sjöström et al. 2001). Specifically, repetitive presentation of a presynaptic spike followed closely by a postsynaptic spike induces LTP. Conversely, if the presynaptic spike succeeds the postsynaptic action potential, long-term depression (LTD) ensues. This form of plasticity has come to be known as spike-timing-dependent plasticity (STDP; for reviews see Abbott and Nelson 2000; Bi and Poo 2000). In addition to the order of activation, STDP is sensitive to the interspike interval (ISI) between action potentials in the pre- and postsynaptic cells. Short intervals produce maximal plasticity, while longer intervals produce little or no change in synaptic strength. The resultant function relating plasticity to ISI exhibits a sharp discontinuity at zero, where differences of only a few milliseconds determine whether maximal LTP or LTD is induced (Bi and Poo 1998; Zhang et al. 1998; Feldman 2000). A simple schematic of STDP is represented in Fig. 1. Intervals defined by post-then-presynaptic pairings will be referred to as negative ISIs, while pre-then-postsynaptic activity will be referred to as positive ISIs.

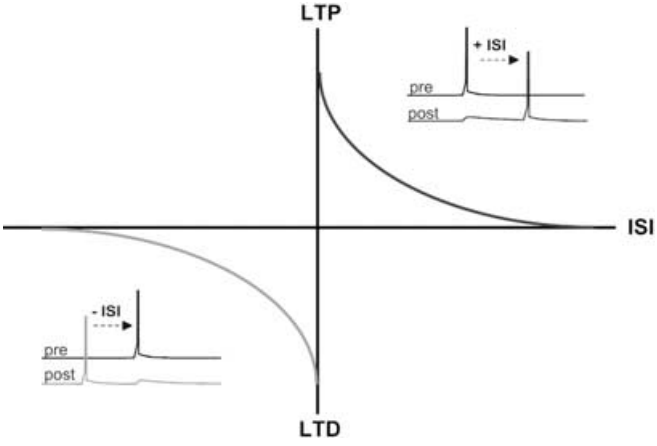

Fig. 1. Schematic of order-specific spike-timing-dependent plasticity (STDP) function. As illustrated by the *inset traces*, presynaptic activity followed by postsynaptic activity (positive interspike interval; *ISI*) produces long-term potentiation (*LTP*), while post- followed by presynaptic activity (negative ISI) produces long-term depression (*LTD*). Maximal plasticity in both directions is produced at ISIs close to zero

STDP protocols have generally consisted of pairing single pre- and postsynaptic spikes. However, presynaptic activity preceding or following a postsynaptic burst can also produce LTP or LTD respectively (Debanne et al. 1994). A fundamental question that stems from this is whether the relationship of plasticity to ISI is itself dependent on the number of postsynaptic spikes. The experiments by Debanne et al. (1994) in organotypic hippocampal slices suggest that this is indeed the case. To determine if this is the case in other brain areas, we performed similar experiments in the cortex. An example of STDP induced with postsynaptic bursts is shown in Fig. 2. In these experiments, a 50-ms postsynaptic burst in auditory cortex layer II/III pyramidal neurons was simultaneously paired with activation of two pathways: one pathway was activated 10 ms before the burst, while the second pathway was activated

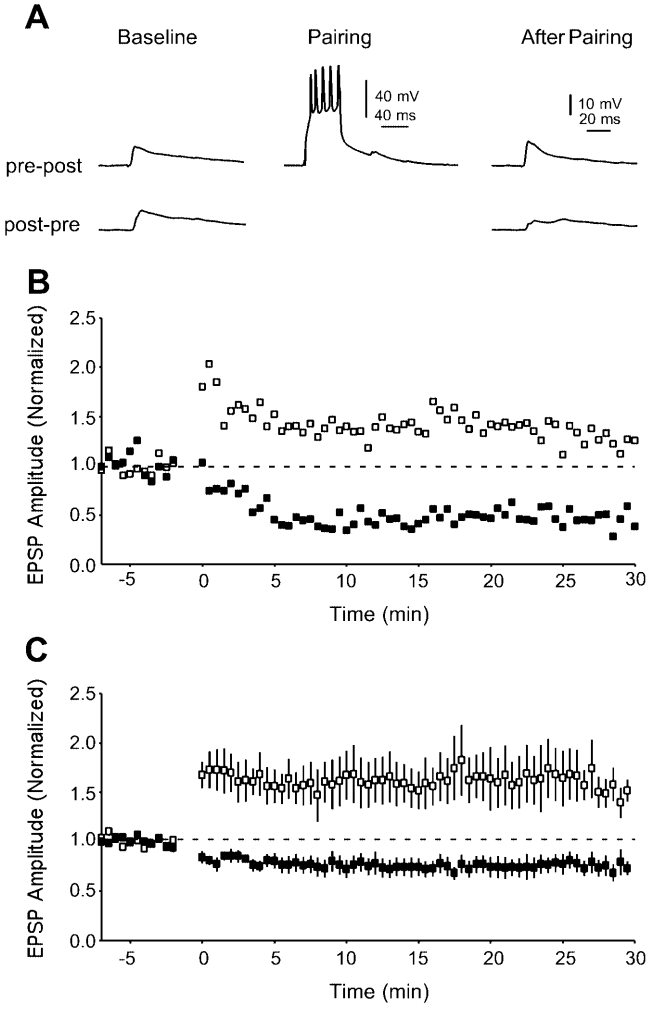

Fig. 2A–C. Example of STDP in auditory cortex with postsynaptic bursts. **A** Representative traces from a single two-pathway experiment. Both pathways were paired simultaneously with the same postsynaptic burst. One pathway was stimulated 10 ms before the burst (*pre–post*) while the other pathway was stimulated 40 ms after the burst (*post–pre*). **B** Full time course of the experiment shown in **A**. Pairing/training took place at 0 min. *Open squares* represent pre–post pathway; *closed squares* represent post–pre pathway. **C** Average data for seven experiments (*error bars* represent SEM)

40 ms after the burst. The results of the burst data show that a pre-before-post pairing produced LTP while a post-before-pre pairing produced LTD simultaneously in the same cell. The average data from seven experiments is shown in Fig. 2C. These data suggest that STDP is indeed pathway specific, and as such is particularly relevant as an example of Hebbian plasticity. Additionally these data indicate that a mechanism for STDP must be compatible with LTD and LTP induced by pairing presynaptic inputs with bursts as well as single spikes.

The potential importance of STDP lies in the fact that it addresses both of the questions left open by Hebb: (i) it establishes a critical time window in which pre- and postsynaptic activity must occur in order to produce long-term changes in synaptic strength, and (ii) it provides a simple learning rule for decreases in synaptic strength.

1.3 Mechanisms underlying STDP

Considerable emphasis has been placed on elucidating the mechanisms underlying associative LTP. In addition to providing a molecular description of LTP, these efforts have advanced our understanding of its functional role. Similarly, determining the mechanisms underlying STDP will further our understanding of its function, and reveal whether it is a robust, computationally relevant phenomenon.

Since STDP exhibits LTD and LTP components, it is reasonable to speculate that it may use the same mechanisms known to underlie associative LTP (Kelso et al. 1986; Wigström et al. 1986) and homosynaptic LTD (Dudek and Bear 1992; Mulkey and Malenka 1992). Associative LTP depends on NMDA receptors (NMDARs), which function as coincidence detectors of pre- and postsynaptic activity. A presynaptic spike results in the release of glutamate, which binds to the NMDAR. Subsequent depolarization caused by a postsynaptic spike produces a voltage-dependent expulsion of Mg^{2+}. Only when both of these events occur in close temporal proximity will the NMDA channels allow the influx of Ca^{2+}. Since glutamate can remain bound to the NMDAR for tens of milliseconds, a postsynaptic spike occurring 15 ms after a presynaptic one can still cause a supralinear Ca^{2+} influx. This is a plausible mechanism for STDP, as both the interval and order sensitivity would then arise from the properties of the NMDAR.

The mechanisms underlying the induction of homosynaptic LTD are more complex. While low-frequency stimulation (LFS) can produce an NMDAR-independent form of LTD that depends solely on metabotropic glutamate receptors (mGluR; Oliet et al. 1997), LTD induced by LFS generally depends on NMDARs (Dudek and Bear 1992; Mulkey and Malenka 1992). NMDAR-dependent LTD can also be induced by pairing presynaptic stimulation with moderate depolarization that is thought to partially open NMDA channels (Cummings et al. 1996, Ngezahayo et al. 2000). This data is consistent with what will be referred to as the "standard model" of long-term plasticity, which holds that moderate levels of Ca^{2+} above baseline induce LTD, while high levels cause LTP (Lisman 1989). It is not known whether these same NMDAR-based mechanisms can account for the order and interval sensitivity of the LTD component of STDP. Specifically, it is unclear why an NMDAR-based model would produce little or no LTD at long negative ISIs and maximal LTD at short ones. In both cases, the membrane of the postsynaptic cell should have returned to close to its resting potential before glutamate is released from the presynaptic terminal. Therefore, any mechanistic description of STDP must address how coincidence detection can take place at negative ISIs.

2 Models of STDP

A fundamental question is whether the standard model of plasticity (Lisman 1989) can account for the order and interval sensitivity of both spike-timing-dependent depression and potentiation. The standard model states that large increases in Ca^{2+} result in LTP while moderate increases produce LTD. In the context of STDP, it is unclear how negative pairing (post-before-pre) intervals could produce these low levels of Ca^{2+} influx. This result may be accomplished by a lasting depolarization after the postsynaptic spike. It may also be that STDP is caused by some variation of the standard model that still requires a single coincidence detector (see Sect. 2.2), or that additional mechanisms such as a second coincidence detector are necessary to describe this phenomenon (Karmarkar and Buonomano 2002).

2.1 Afterdepolarization model

We developed a computational model which incorporates the known associative properties of the NMDAR and the assumptions of the standard model to determine whether it could in theory accurately describe STDP (see the Appendi). Any model of STDP must account for how the cell detects the timing of the post–pre interval. One possibility hinges on the presence of a postsynaptic spike afterdepolarization (ADP). The term ADP refers to the time that the postsynaptic cell remains depolarized after a spike, which is primarily determined by the kinetic properties of the cell's potassium currents and its membrane time constant. It is well established that it is possible to induce LTD by pairing single spikes with moderate postsynaptic depolarization (around −40 mV), and that this form of LTD is NMDA dependent (Cummings et al. 1996; Ngezahayo et al. 2000). It is possible that the LTD component of STDP may result from pairing presynaptic activity with moderate depolarization in the form of the ADP. Indeed, in several published reports on STDP, the action potentials recorded in the soma seemed to exhibit a large ADP,

ranging from 20 to 40 ms (Nishiyama et al. 2000; Normann et al. 2000) and up to 100 ms (Feldman 2000). ADPs are also apparent in recordings of backpropagating action potentials made in dendrites both distal and proximal to the cell body (Magee and Johnston 1997).

This model is centered on the assumption that a postsynaptic action potential produces an ADP that lasts on the order of tens of milliseconds, which has been implemented with an initial magnitude of 6 mV. Figure 3A gives a representation of the postsynaptic voltage response and Ca^{2+} influx at ISIs of -15 and $+15$ ms. The traces also show the peak total Ca^{2+} for the two ISIs. The peak Ca^{2+} level is significantly higher for the $+15$ ms interval due to the NMDAR response to simultaneous binding of glutamate and depolarization (Fig. 3A, black line). The slower positive voltage component of the spike, which can be seen in the voltage traces (Fig. 3A, gray lines), serves as a persistent record of postsynaptic activity. An example of the interaction of the ADP with the excitatory postsynaptic potential (EPSP) at negative ISIs can be discerned in the voltage trace for the -15 ms ISI, and allows for moderate increases in Ca^{2+} influx above those expected for an unpaired EPSP.

The peak Ca^{2+} values recorded for each ISI produce the relationship depicted in Fig. 3B. There is a clear increase in Ca^{2+} concentration from negative to positive ISIs that declines again at long positive intervals. If the Ca^{2+} pool is solely responsible for producing LTD at negative intervals as well as LTP at positive intervals, the model must be constrained so that the Ca^{2+} level at the 0-ms ISI is the LTD/LTP threshold. The Ca^{2+} values below this threshold at negative ISIs should translate to depression and then transition, so that those values above the threshold cause potentiation. It is possible to design a function relating peak Ca^{2+} to plasticity that satisfies these requirements for this model (Fig. 3C).

Combining the relationships in Fig. 3B and C results in the plasticity–ISI function shown in Fig. 3D. Though LTD and LTP are observed at the expected negative and positive intervals respectively, LTD is also observed at some long positive intervals. This departure from the order specificity depicted in Fig. 1 is predictable from the plot of Ca^{2+} versus ISI (Fig. 3B), which shows that

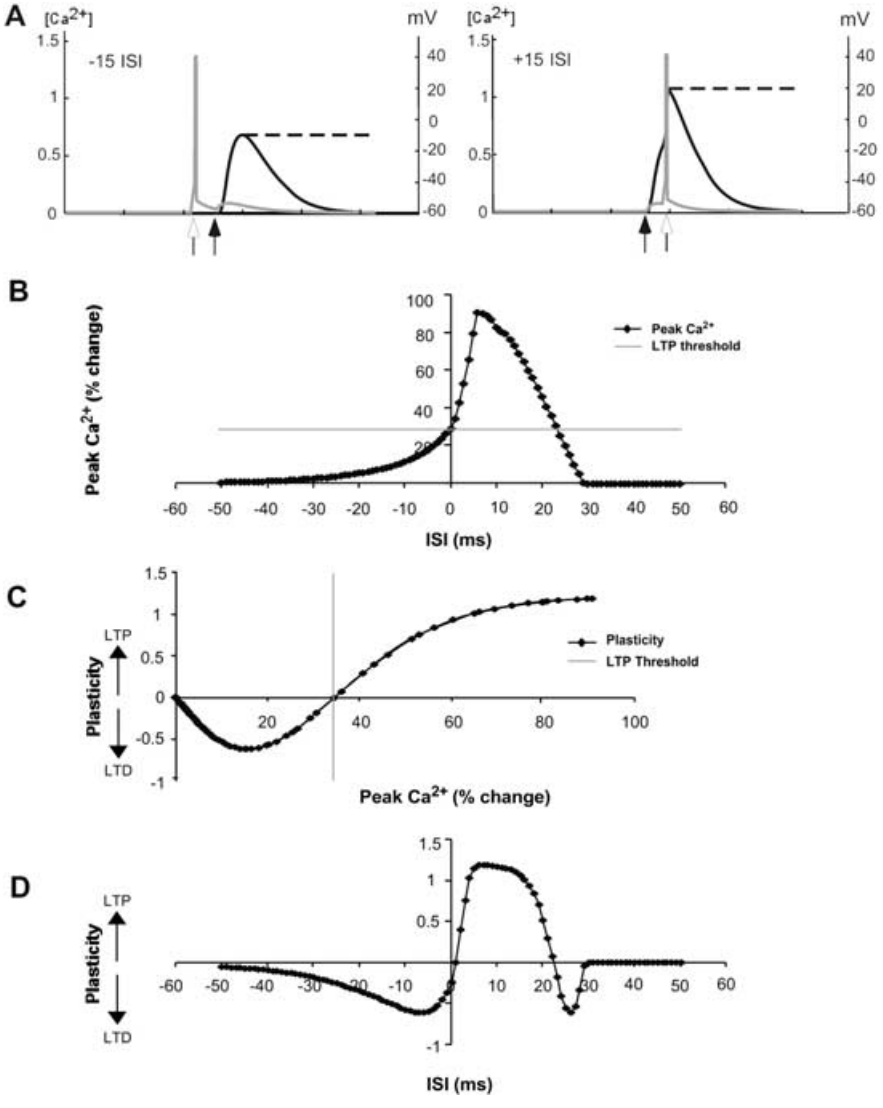

Fig. 3A–D. The afterdepolarization (ADP) model predicts LTD at both positive and negative intervals. **A** Representative Ca^{2+} concentrations (*black lines*) and postsynaptic voltage responses (*gray lines*) as computed in the model for a -15 ms (*left panel*) and a $+15$ ms (*right panel*) ISI. The peak Ca^{2+} influx (*dashed line*) is used as the model output for each ISI. *Filled arrows* indicate EPSP onset; *open arrows* indicate postsynaptic spike onset. Note in the -15 ms ISI voltage trace that the spike ADP overlaps the EPSP. **B** Graph of percentage change above baseline in peak Ca^{2+} values for each ISI from -50 to $+50$ mV. The *gray line* indicates the Ca^{2+} level above which LTP is induced. **C** Plot of plasticity as a function of percentage change in peak Ca^{2+}. The *gray line* indicates the same Ca^{2+}value from **B** which determines the LTP threshold, or the point at which this function crosses the *x*-axis. **D** STDP curve determined by applying the plasticity-vs-Ca^{2+} function (**C**) to the model's Ca^{2+} output as a function of ISI (**B**). Arbitrary units are used for Ca^{2+} and plasticity measurements

the Ca^{2+} concentration decreases smoothly as the positive interval duration increases, and will fall within the range that produces LTD. Since the relationship between relative Ca^{2+} levels and plasticity is an explicit part of the standard model, this conclusion is a general property of the standard model. Interestingly, some experimental evidence has revealed a plasticity-versus-ISI function with LTD at positive and negative intervals (Nishiyama et al. 2000; see discussion in Sect. 2.3).

Additionally, this model suggests that STDP will be strongly dependent on the magnitude and duration of the ADP. Note that it is the ADP and the voltage dependency of the NMDAR that is primarily responsible for LTD at negative intervals. Consequently, changes in the ADP can alter the temporal profile of STDP. This is illustrated in Fig. 4, which shows the results of recalculating the model for a larger ADP of 12 mV, as well as for a spike without an ADP. The 6 mV ADP results from Fig. 3 are also included here for reference. The magnitudes of the ADPs for the three conditions are illustrated in Fig. 4A. Figure 4B shows that changes in the magnitude of the ADP produce changes in the relationship between peak Ca^{2+} and ISI. Specifically, at the negative ISIs, the larger ADP reaches the LTP threshold while removal of the ADP eliminates any change in Ca^{2+} influx. This has distinct consequences for the relationship of plasticity to ISI (calculated via the Ca^{2+}-plasticity function in Fig. 3C) as shown in Fig. 4C. Both conditions disrupt the shape of the temporal profile, with a larger ADP producing LTP at negative intervals, and the lack of an ADP producing LTD only at positive intervals. Similarly, it is important to note that the length of the temporal window that produces LTD will be determined by the duration of the ADP. Thus, a second prediction of this model is that STDP will be sensitive to the shape of the ADP, and more specifically elimination of the ADP will tend to decrease or eliminate the LTD component of STDP.

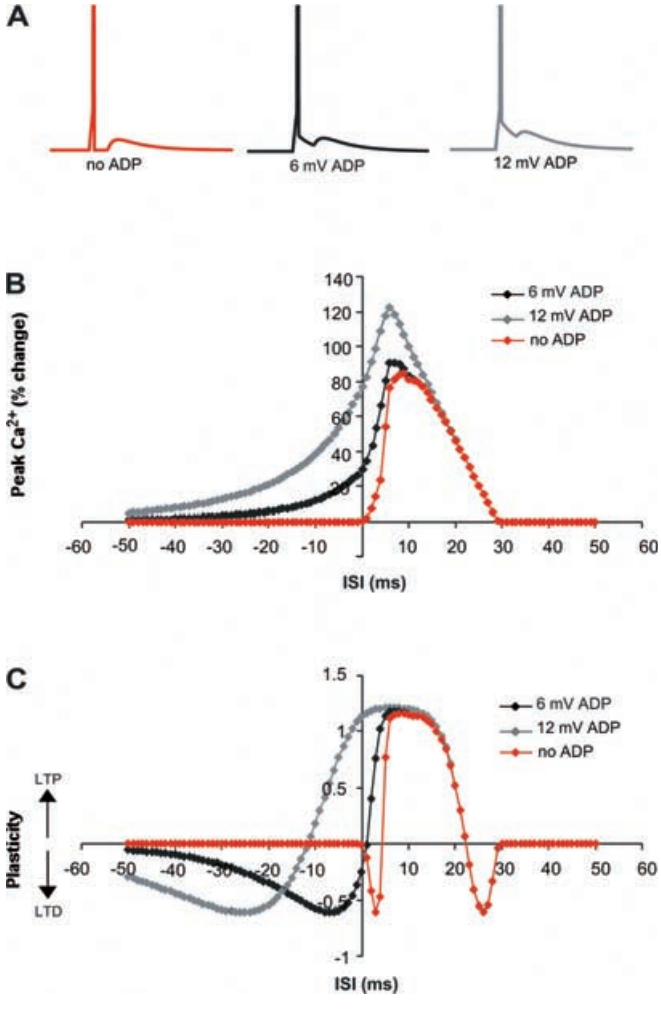

Fig. 4A–C. The ADP model predicts that STDP is sensitive to ADP shape. **A** Representative traces from the ADP model when the magnitude of the ADP is increased to 12 mV (*red line*), for the ADP used in the calculations of Fig. 3 (*black line*), and no ADP (*gray line*). **B** Graph of percentage change above baseline in peak Ca^{2+} values for each ISI from −50 to +50 mV. The *black values* are identical to those in Fig. 3B. **C** STDP (plasticity as a function of ISI) curves calculated using the function represented in Fig. 3C. Changes in the size of the ADP, when all other variables remain constant, cause fundamental changes in the resultant temporal profile of STDP

2.2 Alternative models of STDP

Other models may address both the dependence of the previous model on the ADP as well as its prediction of LTD at both positive and negative intervals. These include both models that also rely on a single coincidence, detector and two, coincidence, detector models.

2.2.1 NMDA/voltage-gated Ca^{2+}-channel model. A model similar to the one in Sect. 2.1 keeps the assumptions of the standard model, but considers the contribution of postsynaptic voltage-gated Ca^{2+} channels (VGCCs) in determining plasticity (Karmarkar and Buonomano 2002). Calcium from VGCCs has been shown to be required for both NMDA- and non-NMDA-dependent spike-timing-dependent depression (Bi and Poo 1998; Normann et al. 2000). Since a backpropagating action potential in the postsynaptic cell allows for Ca^{2+} entry through these channels, it is possible for this Ca^{2+} to provide the necessary signal for LTD. This can work together with the ADP, which would then allow increased Ca^{2+} in through the VGCCs and through the NMDA channels. One potential outcome of including VGCC-dependent Ca^{2+} in this model is that under certain conditions it may be possible for the model to predict plasticity in the absence of a presynaptic stimulus. There is some experimental support for NMDA-independent induction of LTP by voltage-gated Ca^{2+} in the amygdala (Weisskopf et al. 1999), and possibly in synapses proximal to the soma of hippocampal neurons (Magee and Johnston 1997). The implication in the hippocampal data, however, is that in the absence of a presynaptic signal which acts to enhance the amplitude of the postsynaptic action potentials in the dendrites, the spikes are too weak to produce a significant increase in calcium, particularly as they propagate further from the cell body.

LTD in this model is less dependent on the presence of an ADP as voltage-gated Ca^{2+} can act alone as the postsynaptic signal required for LTD induction in the absence of one. However, since this model is also dependent on moderate and high levels of Ca^{2+} to induce LTD/LTP, it produces LTD at some positive intervals for the same reasons described in Sect. 2.1 for the ADP model. Additionally, the relationship of plasticity to ISI will be sensitive to the number of postsynaptic spikes, with negative ISIs potentially producing LTP when plasticity is induced with multiple postsynaptic spikes (Karmarkar and Buonomano 2002).

2.2.2 Afterhyperpolarization model. Another potential mechanism that relies on the NMDAR as the single coincidence detector assumes that LTD could be produced by decreases in Ca^{2+} influx (Linden 1999). This type of model is based on the assumption that rather than an ADP, the spike may actually show an afterhyperpolarization (AHP). In this case, a drop in the cell membrane potential would be interacting with the following EPSP during negative pairing intervals. Therefore, one might suggest that Ca^{2+} levels below those elicited by a baseline EPSP result in depression, while large increases in Ca^{2+} influx result in LTP. This type of mechanism would allow for order-specific plasticity, as Ca^{2+} levels would only drop below baseline during post–pre pairings. However, this mechanism is very sensitive to initial baseline EPSP size, a parameter that varies significantly between cells. Additionally, there is little evidence for decreases in Ca^{2+} producing LTD, and experiments performed by Feldman (2000) suggest that reductions in the AHP do not alter LTD at a -50 ms ISI.

2.2.3 Two-detector model. STDP has also been proposed to rely on a mechanism that uses two coincidence detectors, and thus not reliant on the assumptions of the standard model (Karmarkar and Buonomano 2002). As in the standard model, this "two-detector" model assumes that Ca^{2+} entering through the NMDA channels causes LTP and its timing sensitivity. LTD, however, is determined through a second association point that detects the interaction between a glutamate-activated pathway and the Ca^{2+} entering through the VGCCs due to the postsynaptic spike. Similarly, a model presented by Senn et al. (2000) also essentially relies on distinct coincidence detectors, except that in this case they are represented as two functionally independent states of the NMDAR.

We have proposed that the second coincidence detector may rely on the mGluR pathway (Karmarkar and Buonomano 2002). Experimental data from acute hippocampal slices support a mechanism for LTD based on Ca^{2+}-dependent modulation of the mGluR-mediated pathway (Normann et al. 2000). In this model, the LTD-inducing response depends on the amount of calcium from the VGCCs present at the time that the glutamate-dependent pathway is activated. The interval sensitivity of this response is derived from the Ca^{2+} decay rate. The mechanism would produce plasticity in a manner similar to the mGluR-dependent LTD that has also been seen in response to LFS (Oliet et al. 1997), and would not necessarily require an NMDAR component. Alternately, it could be possible that the NMDARs would play a part as a gating mechanism for LTD as well.

The benefit of a model that incorporates two coincidence detectors is that it is possible to produce robust order-sensitive STDP. Since pre–post and post–pre activity would be mediated by separate mechanisms, there would be no a priori reason for positive intervals to recreate the conditions that produce LTD. The resulting temporal profile would be similar to that of the schematic in Fig. 1, where maximal plasticity of either type is produced by short ISIs, and LTD is only induced by negative pairing intervals. It is also important to note that the model is *not* sensitive to the specific shape of the action potential, nor is it affected by small changes in the relative size of the EPSP, both of which could vary from cell to cell. Since the coincidence detection discriminates pre–post from post–pre activity through different mechanisms, this type of model can reasonably account for order-specific STDP induced with a protocol similar to that shown in Fig. 2 which uses bursts of postsynaptic spikes (Karmarkar and Buonomano 2002). In this aspect, it is more physiologically robust than the single-coincidence-detector models.

2.3 Physiological relevance

While the standard model can account for a type of STDP, it predicts that LTD should be observed at some positive intervals. Indeed, there is some evidence of LTD at positive ISIs in acute hippocampal slices Nishiyama et al. (2000), but not in other reports. It is possible, due to the relatively coarse resolution of some of the plasticity-versus-ISI functions, that LTD under some pre-before-post conditions has been missed. Additionally, intertrial variability of the ISI at positive intervals in vivo might mask LTD. The standard model also predicts that the STDP function will be strongly dependent on the ADP. Fluctuations in the ADP can significantly alter the direction and magnitude of plasticity at a particular ISI, particularly for negative intervals (Fig. 4C). Again, the high ISI variability observed in vivo may decrease the impact of this sensitivity, but on average the STDP function would still detect changes in the ADP. Some experimental data (Sjöström et al. 2001) shows that at least under specific circumstances, LTP may be critically dependent on the ADP. It is also possible that methodological differences that affect ADP shape may account for some differences in experimental results. For example, Pike et al. (1999) showed, using sharp electrodes, that single postsynaptic spikes were not sufficient to induce LTP in CA1 neurons; instead, postsynaptic bursts were required (see also Thomas et al. 1998). This was also our observation in the cortical experiments shown in Fig. 2. In contrast, Nishiyama et al. (2000) obtained LTP with single spikes. However, the whole-cell solution used in the experiments

was Cs^+ based, which produces a long-lasting ADP since K^+-dependent repolarization is blocked, thus in effect producing a postsynaptic burst.

If STDP is sensitive to experimental parameters such as the ADP, rate of stimulation, and EPSP amplitude (Markram et al. 1997; Bi and Poo 1998; Sjöström et al. 2001), then its functional significance may be limited since it may only occur under restricted conditions. It is clear, however, that some forms of STDP are not dependent on an ADP (Debanne et al. 1994, 1998; Zhang et al. 1998), do not seem to exhibit LTD at positive intervals, and may be less sensitive to parameters such as stimulus rate. We suggest that the standard model cannot account for these forms of STDP and that they are most likely best accounted for by a two-coincidence-detectors model (Karmarkar and Buonomano 2002).

3 In vivo correlates of STDP

Ultimately, the functional relevance of STDP will rely on whether or not it is observed in vivo. While most experiments to date have been performed in slices, there is evidence for STDP in vivo as well. Levy and Steward (1983) showed that the order of activation of the ipsi- and contralateral perforant pathways determined whether LTP or LTD was induced in anesthetized rats, and Zhang et al. (1998) described STDP in the intact tadpole. Additionally, recent experiments support a physiological function of STDP by showing that the order of presentation of physiological stimuli or electrical stimulation of the intact brain influence cortical plasticity; these are discussed in Sect. 3.1.

3.1 Cortical plasticity and stimulus order

If STDP were physiologically relevant, it would be expected that certain forms of experience-dependent plasticity would exhibit order sensitivity. Indeed, recent in vivo experimental results indicate that cortical plasticity is also sensitive to the timing of stimuli. Bao et al. (2001) have shown that auditory cortical representations can be changed by pairing a tone with electrical stimulation of the ventral tegmental area (VTA). If tone presentation precedes VTA stimulation by 500 ms, increases in cortical area devoted to that frequency are observed. In contrast, if tone presentation follows VTA stimulation by 500 ms, decreases are observed. Studies in the visual system have also observed order-dependent effects of stimulus presentation. Yao and Dan (2001) showed in anesthetized cats that multiple presentations of two consecutive bars of different orientations (each lasting approximately 8 ms) produced a shift in the orientation of V1 cells. The direction of the shift was predicted by the order of stimulus presentation. If we define the preferred orientation of the cell as S_0, and S_{+15} as an orientation 15° clockwise from the preferred one, then presentation of bars in the order $S_{+15} \rightarrow S_0$ produced a shift in cell orientation selectivity towards S_{+15}, whereas $S_0 \rightarrow S_{+15}$ produced a shift in the opposite direction. In a related experiment, Schuett et al. (2001) paired oriented bars with electrical stimulation of V1 in anesthetized cats. Specifically, stimuli were paired with electrical stimulation with a 65 ms interval (≅20 ms after the stimulus would be expected to produce firing). Intrinsic optical imaging revealed that the sites near the stimulating electrode increased their responses to the paired orientation. In contrast, shorter intervals resulted in decreases in cortical areas activated by the paired orientation.

These studies are consistent with Hebb's original proposal that paired activation of pre- and postsynaptic neurons will enhance the response to the presynaptic cell. However, these studies go a step beyond Hebb, by showing that presynaptic activity following postsynaptic activity can produce a decrease in the response to presynaptic activity. Importantly, these results are consistent with a functional role for STDP.

4 Conclusions

The standard model of LTP/LTD (Lisman 1989) can generate a type of STDP with a specific temporal profile. In this model, the LTD component of STDP depends on pairing presynaptic activity with moderate depolarization of the postsynaptic cell. This depolarization relies on the presence of an action potential ADP, which becomes a fundamental part of the model. Indeed, it seems that much of the published data on STDP exhibits a significant ADP component. A prediction of our ADP model is that artificial removal of the ADP through hyperpolarization should dramatically decrease the LTD component of STDP. As discussed in Sect. 2.1, another prediction of the standard model is that LTD will be observed at some positive intervals. However, at least one report – in acute hippocampal slices (Nishiyama et al. 2000) – has described such a dual LTD component. It is also possible that more precise plasticity-versus-ISI functions will reveal a second LTD component in other preparations. Thus, at least in one case, we would argue that STDP is based on the relative increases in Ca^{2+} entering through the NMDA channels as stated in the standard model. However, this conclusion is accompanied by the caveat that this form of STDP may be highly dependent on experimental parameters, and as a result may not play an important physiological role.

In contrast, it is clear that there are some experiments in which the LTD component does not rely on an ADP. In particular, the experiments of Debanne et al. (1994, 1998) in organotypic hippocampal slices, and of Zhang et al. (1998) in tadpole describe an order-dependent LTD in the apparent absence of any ADP, or in the presence of a clear AHP. We suggest that two mechanistically distinct forms of STDP exist. This second form observed in the absence of ADPs may be more robust, as the balance between LTD and LTP and the temporal profile of the plasticity is not dependent on replicating the exact shape of the action potential. We propose that this strictly order-specific STDP of the type represented

in Fig. 1 does not rely on the standard model, but may require a second coincidence detector in addition to the NMDAR (Karmarkar and Buonomano 2002).

Appendix

A.1 Cortex slice experiments

Slice preparation and whole-cell recording in the auditory cortex was performed in the manner described previously (Buonomano 1999). Briefly, auditory cortex slices were prepared from 12- to 18-day-old Sprague–Dawley rats. Recordings were made at 30 °C in artificial cerebrospinal fluid composed of (mM): NaCl, 58.4; KCl, 74.56; $MgSO_4$, 246.5; NaH_2PO_4, 138; dextrose, 180.2; and $CaCl_2$, 147. Slices were chosen based on the location of the medial geniculate nucleus, visible in the plane of the slices containing the auditory cortex. Whole-cell recordings were made from pyramidal neurons in area II/III. The mean membrane potential and input resistance were 70.8 ± 2.6 mV and 163.3 ± 20.9 MΩ (mean ± SEM), respectively. Recording electrode resistance was 8–10 MΩ and contained one of two intracellular solutions (mM): (i) K-gluconate, 100; KCl, 20; ATP-Mg, 4; phosphocreatine, 10; GTP, 0.03; Hepes, 10; pH 7.3; or (ii) KCL, 60; ATP, 5; Na-phosphocreatine, 10; $MgCl_2$, 5; EGTA, 0.6; GTP, 0.3; HEPES 30; methane sulfonate, 40. Two independent pathways in layer II/III were stimulated at an intensity of 25–250 nA on either side of the recording electrode.

EPSPs were produced alternately by the two pathways every 15 s during testing. Training began after a minimum baseline of 5 min. The experiment used a simultaneous pairing protocol in which both pathways were paired with a burst of spikes during training: one with a positive ISI, one with a negative ISI. Specifically, the training protocol consisted of an EPSP evoked in one input pathway followed 10–15 ms later by a 40- to 50-ms burst of spikes in the cell, which was then followed 35–50 ms later by an EPSP evoked from the other pathway. The spike burst was produced with a depolarizing pulse of 40–50 ms duration. This pairing was applied 100 times at 1 Hz. Although the pairing frequency was not varied parametrically, there did not appear to be a threshold effect as seen by Markram et al. (1997). Following training, recordings of the test pulses resumed for at least 30 min.

A.2 ADP model

The pre- and postsynaptic cells were modeled as single compartment integrate-and-fire units with an E_{leak} of −60 mV. Action potentials in the postsynaptic cell were induced by a 3-ms depolarization of the membrane above the spike threshold of −40 mV. Membrane voltage was reset to −54 mV after a spike to produce the 6 mV ADP (and set to −48 and −60 mV to produce the 12 mV ADP and no-ADP conditions depicted in Fig. 4). The time that it took the membrane to repolarize was determined by the membrane time constant of 20 ms. All simulations were conducted with the modeling program NEURON (Hines and Carnevale 1997).

The cells were connected by an excitatory synapse with both AMPA and NMDA receptors. Activation of these receptors was simulated with "kinetic synapses" (Destexhe et al. 1993). Synaptic transmission occurred during a brief pulse of a fixed duration; during a pulse the binary variable for glutamate (C) is set to 1, and receptor activation $R(t)$, which is proportional to synaptic conductance, follows

$$R(t - t_{on}) = R_\infty + [R(t_{on}) - R_\infty] \exp[-(t - t_{on})/R_\tau] \tag{A1}$$

After a pulse, $R(t)$ is determined as

$$R(t - t_{off}) = R(t_{off}) \exp[-\beta(t - t_{off})] \tag{A2}$$

where t_{on} and t_{off} represent the onset and offset of the pulse, and the duration of the pulse is 1 and 5 ms for the AMPA and NMDA currents, respectively. R_∞ and R_τ are defined as follows:

$$R_\infty = \frac{\alpha C}{\alpha C + \beta} \tag{A3}$$

and

$$R_\tau = \frac{1}{\alpha C + \beta} \tag{A4}$$

Both AMPA and NMDA receptors kinetics are modeled by these equations. The constants determining the binding (α) and dissociation (β) of glutamate to the postsynaptic receptors were (Buonomano 2000)

AMPA	NMDA
$\alpha = 0.5\,\text{ms}^{-1}$	$\alpha = 0.072\,\text{ms}^{-1}$
$\beta = 0.25\,\text{ms}^{-1}$	$\beta = 0.075\,\text{ms}^{-1}$

The Ca^{2+} influx through the NMDA channels is dependent on the membrane voltage and presence of bound glutamate. The Mg^{2+} block of the NMDA channels is modeled as a sigmoidal voltage-dependent function:

$$B(v) = \frac{1}{1 + \exp[0.0868(-v - 10)]} \tag{A5}$$

approximated from Bekkers and Stevens (1993). The glutamate dependence, R_{NMDA}, is calculated as described above. The change in NMDAR Ca^{2+} entering the cell (Ca^{2+}_{NMDAR}) is calculated using these terms, the driving force, and the Ca^{2+} decay rate τ:

$$\frac{dCa^{2+}_{NMDAR}}{dt} = -0.008(v - 140)\left[B(v)\frac{R_{NMDA}}{0.6178}\right] - \frac{Ca^{2+}_{NMDAR}}{\tau} \tag{A6}$$

To determine Ca^{2+} as a function of ISI for this model, the maximum value of Ca^{2+}_{NMDAR}, Ca_{peak} was recorded at each ISI. Peak Ca^{2+} is the factor used as the signal for plasticity. This parameter reflects the importance of the

increase in calcium at the time of interaction between pre- and postsynaptic activity for both positive and negative ISIs, as well as the relative magnitudes that produce degrees of plasticity. While this measure can extend to the simulation of more complex firing patterns that produce STDP (Karmarkar and Buonomano 2002), it is not specifically designed to account for induction paradigms that require Ca^{2+} integration over multiple trials.

The equation describing plasticity (P) as a function of peak Ca^{2+}, as plotted in Fig. 3C, is represented as follows, with $k_1 = 0.02$:

$$P(Ca^{2+}_{peak}) = 2.8\left[\frac{1}{1+e^{12(-Ca^{2+}_{peak}+k_1)}}\right] - 2.7\left[\frac{1}{1+e^{(-20Ca^{2+}_{peak})}}\right] + 1.117 \qquad \text{(A7)}$$

Pairing was simulated by eliciting an action potential in each cell at ISIs ranging from -50 to $+50$ ms. ISIs were defined by the onset time of the first event to the onset time of the second event.

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