Neuron, Vol. 44, 23–30, September 30, 2004, Copyright ©2004 by Cell Press

Spike Timing-Dependent Plasticity of Neural Circuits

Review

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Recent findings of spike timing-dependent plasticity (STDP) have stimulated much interest among experimentalists and theorists. Beyond the traditional correlation-based Hebbian plasticity, STDP opens up new avenues for understanding information coding and circuit plasticity that depend on the precise timing of neuronal spikes. Here we summarize experimental characterization of STDP at various synapses, the underlying cellular mechanisms, and the associated changes in neuronal excitability and dendritic integration. We also describe STDP in the context of complex spike patterns and its dependence on the dendritic location of the synapse. Finally, we discuss timing-dependent modification of neuronal receptive fields and human visual perception and the computational significance of STDP as a synaptic learning rule.

Since the discovery of persistent enhancement of synaptic transmission by tetanic stimulation in the hippocampus (Bliss and Lømo, 1973), a phenomenon now generally referred to as long-term potentiation (LTP), the study of activity-dependent synaptic plasticity has become an active area in neurobiology (Martin et al., 2000; Malenka and Siegelbaum, 2001). Two features of LTP—the associativity and input specificity—match the properties of some forms of learning and memory, suggesting that LTP may underlie these cognitive functions. Traditionally, LTP is induced by high-frequency presynaptic stimulation or by pairing low-frequency stimulation with postsynaptic depolarization. Prolonged low-frequency stimulation was also found to induce long-term depression (LTD) (Mulkey and Malenka, 1992; Kirkwood and Bear, 1994). Thus, synaptic efficacy can be modified in a bidirectional manner. In studying the temporal specificity of associative synaptic modification in the hippocampus, a region known to be important for memory formation, Levy and Steward (1983) noted that when a weak and a strong input from entorhinal cortex to the dentate gyrus were activated together, the temporal order of activation was crucial: LTP of the weak input was induced when the strong input was activated concurrently with the weak input or following it by as much as 20 ms. Interestingly, LTD was induced when the temporal order was reversed. Recent studies on a variety of excitatory synapses have further addressed the importance of the temporal order of pre- and postsynaptic spiking and have defined the "critical windows" for spike timing (Figure 1), which are on the order of tens of milliseconds (Markram et al., 1997; Magee and Johnston, 1997; Bell et al., 1997; Debanne et al., 1998; Zhang, et al., 1998; Bi and Poo, 1998; Egger et al., 1999; Feldman, 2000; Sjostrom et al., 2001; Boettiger and Doupe, 2001; Froemke and Dan, 2002; Tzounopoulos et al., 2004). This is now referred to as spike timing-dependent plasticity (STDP). More recent experimental studies have further addressed the following questions: What mechanisms underlie the cell type-specific temporal windows for LTP/LTD? Does activity-induced modification of GABAergic synapses depend on the precise timing of pre/post spiking? Is there STDP in neuronal excitability and dendritic integration? How does complex neuronal spiking, including high-frequency bursts, affect STDP? How does STDP affect the operation of neural circuits and higher brain functions such as sensory perception? We here review some recent results pertinent to these questions.

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Cellular Mechanisms

The most striking feature of STDP is the dependence on the temporal order of pre/post spiking. What are the cellular mechanisms underlying this temporal specificity? At many synapses, the induction of spike timing-dependent LTP/LTD requires activation of the NMDA subtype of glutamate receptors (NMDARs) (e.g., Markram et al., 1997; Magee and Johnston, 1997; Debanne et al., 1998; Zhang et al., 1998; Bi and Poo, 1998). In some cases, LTD induction was also shown to require the activation of L-type Ca^{2+} channels (Bi and Poo, 1998) and Ca^{2+} release from internal stores (Nishiyama et al., 2000). A straightforward explanation for the temporally asymmetric STDP is that the relative timing of glutamate binding to NMDARs and the spiking of the postsynaptic dendrite determines the Ca^{2+} level required for either LTP or LTD: Pre→post spiking leads to the opening of NMDARs via depolarization-induced removal of Mg^{2+} block, resulting in a high-level Ca^{2+} influx, whereas post→pre spiking leads to a low-level sustained Ca^{2+} rise by the opening of voltage-dependent Ca^{2+} channels (VDCCs) and/or limited NMDAR activation. Different cascades of signaling events are set in motion by high- and low-level postsynaptic Ca^{2+} for LTP and LTD induction, respectively (Malenka and Siegelbaum, 2001). Fluorescence Ca^{2+} imaging studies indeed demonstrated that Ca^{2+} influx through NMDARs and VDCCs exhibits supralinear summation with pre→post spiking and sublinear summation with post→pre spiking (Koester and Sakmann, 1998). In support of this interpretation, partial inactivation of NMDARs in CA1 hippocampus leads to the induction of LTD, rather than LTP, by the pre→post spiking protocol (Nishiyama et al., 2000). Action potential (AP)-dependent desensitization of NMDARs (Rosenmund et al., 1995; Tong et al., 1995; Umemiya et al., 2001) may also contribute to the reduced Ca^{2+} elevation in the post→pre condition. Taken together, these findings showed that NMDAR is a major player in inducing STDP, although other coincidence detectors cannot be

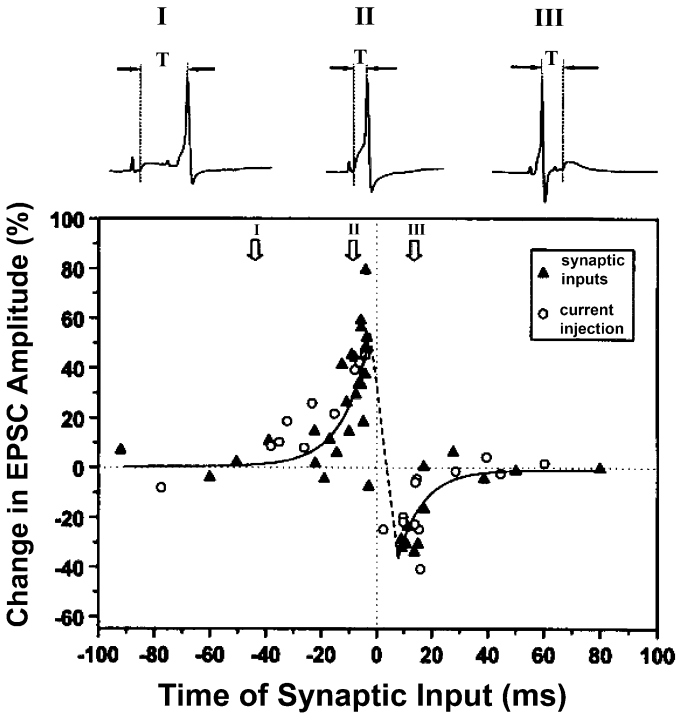

Figure 1. The Critical Window for Spike Timing-Dependent Plasticity of Developing Retinotectal Synapses

The percentage change in the synaptic strength (EPSC amplitude) after repetitive retinal stimulation was plotted against the onset time of the retinal stimulation relative to the peak of the action potential initiated in the tectal cell. Data shown are for experiments in which spiking of the tectal neuron was initiated by either a suprathreshold input or a group of coactive inputs (filled circles) or by injection of a depolarizing current (open circles) in a tectal neuron (from Zhang et al., 1998).

ruled out (Karmarkar and Buonomano, 2002; Sjostrom et al., 2003).

Since both feedforward and feedback GABAergic inhibition will affect dendritic depolarization induced by excitatory inputs and thus modulate postsynaptic Ca^{2+} elevation, the presence of correlated GABAergic inputs onto the postsynaptic neuron may also influence the induction of LTP/LTD (e.g., Wigstrom and Gustafsson, 1986). This notion is further supported by the finding in hippocampal CA1 pyramidal neurons, where the developmental reduction in the effectiveness of spike pairing in inducing LTP can be reversed by blocking $GABA_A$ receptor-mediated inhibition (Meredith et al., 2003).

Another feature of STDP is the variable widths of LTP/LTD windows found in different synapses. The width of the LTP window may reflect (1) the duration over which the glutamate-bound NMDARs can be effectively opened by the spike-induced removal of Mg^{2+} block (Kampa et al., 2004), (2) the nonlinear Ca^{2+} dependence of postsynaptic downstream mechanisms, and (3) the kinetics of EPSP-activated dendritic conductances, e.g., I_A, that modulate the profile of the backpropagating AP (Johnston et al., 2003). For the LTD window, the width may depend on (1) the time course of AP-induced Ca^{2+} influx through VDCCs, which may in turn induce NMDAR desensitization, leading to a reduced NMDAR-mediated Ca^{2+} influx (Froemke and Dan, 2003), (2) the density of transient (I_A) and Ca^{2+}-activated (BK and SK) K^+ channels, which determine the AP profile and thus modulate the NMDAR- and VDCC-mediated Ca^{2+} influx (Watanabe et al., 2002; Shouval et al., 2002), and (3) the duration of AP-triggered secretion of retrograde factors, e.g., endocannabinoids, which act together with presynaptic release of glutamate to induce LTD (Sjostrom et al., 2003). Furthermore, the width and amplitude of the STDP window (Figure 1) may also be modified by neuromodulatory influences due to other converging inputs on the postsynaptic neuron. Activation of β-adrenergic receptors with isoproterenol, for example, widens the window for LTP induction by pre/post pairing in hippocampal CA1 pyramidal neurons (Lin et al., 2003). Such a neuromodulatory effect presumably involves the modulation of NMDARs or dendritic ion conductances, which in turn affects the processes described above.

Much less is known about the expression mechanisms of STDP. Are they similar to those underlying LTP/LTD induced by conventional protocols? Is there modulation of presynaptic transmitter release or postsynaptic glutamate receptors? As discussed below, correlated pre/post spiking can cause persistent changes in both pre- and postsynaptic active conductances, leading to bidirectional modulation of neuronal excitability and dendritic integration of EPSPs. Thus, it is likely that spike timing-dependent LTP/LTD may be expressed both pre- and postsynaptically. Modulation of presynaptic transmitter release has indeed been suggested by a recent study (Sjostrom et al., 2003).

STDP of GABAergic Synapses

While most studies on STDP of synapses focused on glutamatergic synapses, a recent study in rat hippocampal cultures and slices showed that repetitive postsynaptic spiking within 20 ms either before or after the activation of GABAergic synapses led to a persistent change in synaptic strength (Woodin et al., 2003). This effect required Ca^{2+} influx through postsynaptic L-type Ca^{2+} channels and appeared to be caused by decreased activity of a K^+-Cl^- cotransporter, KCC2, which reduced the inhibition by a depolarizing shift of the reversal potential for GABA-induced currents. Thus, GABAergic synapses can be modified by pre/post spiking, allowing the inhibition to be modulated according to the pattern

of postsynaptic excitation, although the temporal window is symmetric.

Global Modification of Intrinsic Neuronal Excitability

Persistent changes in neuronal excitability following repetitive activity have long been noted in the studies of associative learning in various invertebrate and vertebrate model systems (see reviews by Zhang and Linden, 2003; Daoudal and Debanne, 2003). Changes in postsynaptic neuronal firing characteristics can result from modulation of either the excitatory/inhibitory synaptic drive or the membrane conductances (intrinsic excitability). The latter has been reported in many cases. For example, activity associated with trace eyeblink conditioning in rabbits causes an enhanced intrinsic excitability of hippocampal CA1 and CA3 pyramidal cells for a few days, as shown by the reduction in both spike accommodation during prolonged depolarization and post-burst afterhyperpolarization (Moyer et al., 1996). In cerebellar deep nuclei, which are implicated in the trace eyeblink conditioning, brief high-frequency activation of mossy fiber inputs also causes a rapid and persistent increase in the intrinsic excitability (Aizenman and Linden, 2000). Similarly, theta burst stimulation (TBS) of mossy fibers potentiated the intrinsic excitability of granule cells in the cerebellum, an effect that can be dissociated from TBS-induced LTP of mossy fiber-granule cell synapses (Armano et al., 2000). Interestingly, although these changes in intrinsic excitability depend on NMDAR activation, they can occur in the absence of LTP, suggesting a separate downstream mechanism. The immediate changes of intrinsic excitability in all these studies point to a rapid cytoplasmic signaling mechanism that leads to global modulation of ion channels in the neuron.

A form of spike timing-dependent modification of intrinsic neuronal excitability was shown recently in hippocampal cultures, where the induction of LTP/LTD by correlated pre/post spiking was accompanied by an immediate and persistent enhancement/reduction of the intrinsic excitability of the presynaptic neuron (Ganguly et al., 2000; Li et al., 2004). This modification of excitability is temporally specific, with a requirement for pre/post spiking intervals identical to that for LTP/LTD. Such up- and downregulation of excitability is due to the global enhancement of Na^+ and slow-activating K^+ channel activation, respectively, but it requires activation of NMDARs and postsynaptic influx of Ca^{2+}, suggesting that *trans*-synaptic retrograde signaling is involved. Given the rapidity of these presynaptic changes (on the order of minutes) and the requirement for presynaptic PKA and PKC activities, posttranslational modification of Na^+ and K^+ channels is the most likely underlying mechanism. This retrograde presynaptic modification associated with LTP/LTD induction (see above) may involve local conductance changes at presynaptic nerve terminals that modulate the profile of membrane depolarization required for evoking transmitter release, in addition to the modulation of transmitter release machinery. Although such STDP of intrinsic excitability was first observed in cell cultures, similar effects were found in layer 2/3 interneuron-pyramidal cell pairs of somatosensory cortical slices (Li et al., 2004).

Modification of Local Dendritic Excitability and Synaptic Integration

Besides changes in the global presynaptic excitability, correlated activity also results in modification of local postsynaptic excitability. In the original study of Bliss and Lømo (1973), induction of LTP by tetanic stimulation was followed by an increase in the coupling between EPSPs and postsynaptic spiking, an EPSP-to-spike (E-S) potentiation distinct from the enhanced synaptic transmission (see Andersen et al., 1980; Chavez-Noriega et al., 1990; Pugliese et al., 1994). A reduction of tonic inhibitory drive may contribute to the E-S potentiation following LTP induction (Abraham et al., 1987; Chavez-Noriega et al., 1989; Tomasulo and Ramirez, 1993; Lu et al., 2000), but local modification of dendritic conductances is also implicated (Hess and Gustafsson, 1990; Asztely and Gustafsson, 1994; Jester et al., 1995). Recent dendritic patch recordings showed that LTP induction is indeed accompanied by a local modulation of transient A-type K^+ currents that can account for the enhanced excitability associated with E-S potentiation (Frick et al., 2004). In addition to LTP-associated changes, Daoudal et al. (2002) found that LTD was also associated with an NMDAR-dependent, long-lasting E-S depression. This effect is input specific and is expressed when GABA receptors are blocked, suggesting the involvement of a reduction in the intrinsic excitability of the postsynaptic dendrite. In general, the modulation of local active conductances depends on NMDAR activation and represents a direct consequence of LTP/LTD induction, which is known to result in local postsynaptic modulation of transmitter receptors, including their state of phosphorylation and trafficking in and out of the subsynaptic membrane (Malenka and Siegelbaum, 2001). The same postsynaptic biochemical cascades triggered by NMDAR activation thus may act upon both transmitter receptors and voltage-dependent ion channels.

Modulation of local active conductances in the dendrite can influence not only the initiation and propagation of dendritic spikes, but also the summation of synaptic potentials, a critical step in the neuronal processing of information. In hippocampal CA1 pyramidal neurons, a brief period of correlated pre/post spiking that induces LTP and LTD also results in a persistent increase and decrease, respectively, in the linearity of spatial summation of EPSPs (Wang et al., 2003). These modifications are input specific, i.e., they occur only for the summation of the modified input with other inputs on the same postsynaptic dendrite. The increase in linearity was primarily attributed to a local modification of I_h channels, which are known to influence dendritic summation of EPSPs (Magee, 1998, 1999; Cash and Yuste, 1999). These changes in linearity accompanying LTP/LTD help to boost the effects of the synaptic modifications.

Temporal Complexity: Irregular and Burst Spiking

In most in vitro studies of STDP, pre/post spikes were paired repetitively at regular intervals. For neural circuits in vivo, however, spiking in both pre- and postsynaptic cells is likely to be irregular (Softky and Koch, 1993), with occasional high-frequency bursts. How well does the simple STDP learning rule (Figure 1) account for the effects of complex spike patterns? A recent study in

layer 2/3 of visual cortical slices (Froemke and Dan, 2002) measured synaptic modification induced by spike "triplets" of varying intervals and showed that the first spike pair in each triplet played a dominant role and the contribution of the second pair was suppressed. A simple descriptive model that incorporated the suppression effect well predicted the effects of more complex spike patterns, including spike quadruplets and spike train segments recorded in vivo in response to natural stimuli. Interestingly, this suppressive interaction is consistent with the prediction of an adaptive STDP learning rule designed to stabilize the output firing rate of the postsynaptic neuron with changing input rate (Kepecs et al., 2002).

The effects of complex spike trains were also examined in layer 5 of visual cortical slices, using paired bursts of spikes with varying pre/post intervals and firing rates (Sjostrom et al., 2001). In addition to the pre/post interval, synaptic modification was also found to depend on the firing rate within the burst, which was not accounted for by the standard STDP window. The magnitude of LTP, but not LTD, increased with the firing rate; at high firing rates, the pre→post spike pairs appeared to "win over" the post→pre pairs, leading to LTP regardless of the pre/post interval. This finding suggests that with high-frequency bursts synaptic modification is no longer sensitive to the timing of individual spikes, and a burst of spikes may be considered as a basic element in synaptic modification. Consistent with this idea, a recent study in the CA3 region of the hippocampus (Kobayashi and Poo, 2004) showed that LTP of the associational/commissural connections can be induced by pairing spike bursts in the mossy fibers and the association/commissural pathway, and this effect depends on the temporal order and interval between the pre/post bursts rather than individual spikes.

The above studies are beginning to delineate the rules governing the effects of complex spike trains beyond the standard STDP window for isolated spikes. Further studies are needed to determine the biophysical basis and applicability of these rules. There are several additional issues concerning the interaction among multiple spikes in STDP induction. First, the magnitude and persistence of synaptic modification may exhibit nonlinear dependence on the number of induction pairs (pre/post spikes or bursts), with a distinct threshold and a saturation level. Second, the effect may depend on the temporal distribution of the pairs: while synaptic modification may saturate within a single induction episode, a resting period may allow the synapse to recover its sensitivity to additional episodes. Such dependence on the temporal pattern of induction has been demonstrated in the developing *Xenopus* visual system (Zhou et al., 2003), a phenomenon reminiscent of the differential effects of "mass" versus "spaced" learning. Third, the susceptibility of the synapse to modification may depend on the state of the synapse, which can be a function of both the current synaptic strength (Debanne et al., 1996; Bi and Poo, 1998) and the prior history of modification (Montgomery and Madison, 2002). Finally, both STDP and the classical forms of LTP/LTD (e.g., induced by theta burst or low-frequency stimulation) may contribute to normal brain functions, and their relative importance may depend on the neuronal circuits involved and the behavioral context of the animal. Further clarification of these issues is important for understanding the functional implications of STDP in vivo.

Spatial Complexity: Dependence on Dendritic Location

In the central nervous system, each neuron may receive thousands of inputs distributed across an extensive dendritic tree, and postsynaptic processing of the inputs depends strongly on their dendritic locations (Segev and London, 2000; Hausser and Mel, 2003), due to cable filtering and nonuniform distribution of active conductances (Johnston et al., 2003). Is STDP also dependent on the dendritic location of the input? In layer 2/3 of visual cortical slices, STDP windows were measured at different locations along the apical dendrite of the pyramidal neuron (Froemke and Dan, 2003). Both the magnitude and temporal specificity of synaptic modification were found to vary with location: at the distal dendrite, LTP is smaller, while the pre/post window for LTD is broader. The location dependence of the LTD window may be attributed to the difference in the time course of the suppression of EPSPs by the backpropagating APs. Simulation studies suggest that the dendritic inhomogeneity of the STDP window is functionally useful in allowing differential selection of synaptic inputs at distal and proximal dendrites according to the temporal characteristics of the presynaptic spike trains. The importance of domain-specific inputs from inhibitory interneurons has been well recognized (Freund and Buzsáki, 1996; Klausberger et al., 2003; Pouille and Scanziani, 2004), but the functional significance of dendritic localization of excitatory inputs remains to be explored. Given the rich repertoire of dendritic nonlinearity and inhomogeneity, spatial sorting of inputs can significantly enhance the computational capacity of the neuron (Mel et al., 1998; Archie and Mel, 2000). Finally, although in most STDP studies backpropagating APs are evoked in the dendrite, in cells where backpropagating APs do not reach the distal tip of the dendrite, LTP may be induced by local Ca^{2+} spikes resulting from strong synaptic inputs (Golding et al., 2002).

In addition to the pre/post interspike interaction, crosstalk among converging presynaptic inputs may also contribute to STDP. Heterosynaptic interactions may occur at several levels. First, coincident activity of neighboring inputs can directly affect induction of LTP/LTD via cooperative initiation of postsynaptic spiking (Zhang et al., 1998) or by modulating local dendritic conductances that influence the backpropagating AP (Bernard and Johnston, 2003). Second, synaptic modification induced by correlated pre/post activity can cause heterosynaptic changes of either the same (Nishiyama et al., 2000) or the opposite (Royer and Pare, 2003) polarity in a distance-dependent manner. An intriguing possibility is that the spatially inhomogeneous pre/post interactions and the distance-dependent heterosynaptic interactions together shape the dendritic distribution of synaptic inputs in a manner that matches the function of each input for optimal information processing.

STDP of Synaptic Efficacy In Vivo

Most STDP studies were carried out in slices or cell cultures, with a few exceptions. Whole-cell recordings

from developing *Xenopus* tectal neurons in vivo showed that convergent retinotectal synapses undergo STDP with temporally asymmetric time windows (Zhang et al., 1998) resembling those found in hippocampal cultures (Bi and Poo, 1998) and visual cortical slices (Froemke and Dan, 2002). In the kitten visual cortex (Schuett et al., 2001), repetitive pairing of oriented visual stimuli with extracellular electrical stimulation in the cortex induced marked changes in the orientation map—the neuronal orientation preference shifted toward and away from the paired orientation when the cortex was activated visually before and after electrical stimulation, respectively. This dependence of cortical modification on the order of visual and electrical stimulation is consistent with STDP of intracortical connections. Whole-cell recordings in the rat visual cortex showed that visually evoked synaptic responses can be modified by pairing visual stimulation with postsynaptic spiking elicited by the whole-cell electrode (Meliza and Dan, 2004). The direction of the modification depends on the temporal order of the synaptic response and the postsynaptic spiking in a manner that agrees with STDP found in visual cortical slices (Froemke and Dan, 2002). Experience-dependent plasticity of the somatosensory cortical map may also involve STDP. For example, whisker deprivation causes an immediate change of the firing order for L4 and L2/3 neurons, with only modest effects on the firing rate (Celikel et al., 2004). Such a change in relative spike timing may account for whisker deprivation-induced LTD of intracortical excitatory synapses between L4 and L2/3 pyramidal neurons (Allen et al., 2003). Finally, timing-dependent plasticity was also found in the human motor system: repetitive pairing of electrical simulation of the afferent input with transcranial magnetic stimulation (TMS) of the motor cortex induced either potentiation or depression of TMS-evoked potentials, and both the temporal specificity and the pharmacological properties of these changes are consistent with STDP (Wolters et al., 2003).

Compared with in vitro preparations, neural circuits in vivo usually exhibit a higher level of spontaneous spiking, which may influence activity-dependent synaptic modifications. Recordings from free moving adult rats showed that electrically induced LTP in the hippocampus is quickly reversed when the rat enters a novel environment within 1 hr after induction (Xu et al., 1998). In developing retinotectal synapses, LTP and LTD induced by either electrical stimulation (paired spiking or theta bursts) or visual stimuli are rapidly reversed by spontaneous spiking in the tectal neuron or by random visual stimuli (Zhou et al., 2003). This reversal of LTP can be prevented if postsynaptic spiking or NMDAR activation is blocked during the first 20 min after induction, but not afterwards. The susceptibility of LTP and LTD to reversal by physiological spontaneous activity in vivo may account for the short-term nature of STDP of cortical receptive fields and human visual perception (see below). In the retinotectal system, the reversal of LTP can be prevented and stable modification can be achieved by repeating the induction protocol a few times at an optimal spacing (Zhou et al., 2003). Such a requirement for "spaced" induction protocol may prevent accidental pairing of pre/post spikes from producing lasting traces in the neural circuit.

STDP of Receptive Fields and Visual Perception

Whereas most of the above studies used electrical stimulation to control the timing of postsynaptic spiking, other studies have examined STDP under more physiological conditions, using sensory inputs to evoke spiking that is time locked to the stimuli. In adult cat primary visual cortex, pairing of visual stimuli at two orientations induced a shift in orientation tuning, with the direction of the shift depending on the temporal order of the stimulus pair (Yao and Dan, 2001). The induction of significant shift required that the interval between the pair fall within $\pm$40 ms, reminiscent of the temporal window for STDP (Froemke and Dan, 2002). Mirroring the plasticity found in cat visual cortex, similar conditioning also induced a shift in the perception of orientation by human subjects. Since the shifts induced by monocular conditioning exhibit complete interocular transfer, they are likely due to circuit modifications at the cortical level, where visual signals from the two eyes converge substantially. Moreover, a model circuit that exhibits STDP at intracortical connections can account for both the temporal and orientation specificity of the effect (Yao et al., 2004).

Besides the orientation domain, stimulus timing-dependent cortical modification has also been demonstrated in the space domain (Fu et al., 2002). Asynchronous visual stimuli flashed in two adjacent retinal regions were found to control the relative spike timing of two groups of cortical neurons with a precision of tens of milliseconds, and they induced modifications of intracortical connections (as revealed by cross-correlation analysis) and shifts in receptive fields. These changes depended on the temporal order and interval between the stimuli, consistent with STDP of intracortical connections. Parallel to the modifications in cat V1, asynchronous conditioning also induced shifts in perceived object position by human subjects. While the causality between STDP and these receptive field modifications remains to be firmly established, the temporal specificity of STDP provides a unique signature for stimulus-induced cortical modifications at multiple levels, from synapse to perception.

Motion-Induced Synaptic Modifications

The studies reviewed above provide limited insights into how STDP operates during natural visual tasks, since repetitively flashed stimuli are rare in natural scenes. Motion stimuli, which are far more common, can activate neighboring V1 neurons at short temporal intervals and thus may modify their synaptic connections through STDP. A simple model circuit based on STDP predicted that random motion stimuli promote the development of a spatial asymmetry in the intracortical connections made by direction-selective cells (Fu et al., 2004). This asymmetry predicted two novel effects of motion stimuli on receptive field positions, which were confirmed experimentally in adult cat visual cortex. These receptive field properties can largely account for two illusions reflecting the influences of motion on perceived object position. Thus, motion-position interactions in visual perception may be mediated by asymmetric cortical circuits as a natural consequence of STDP during circuit development.

Besides motion signals in the sensory stimuli, locomotion of the animals may also shape the nervous system through STDP. Repeated locomotion of the rat along a linear track induces an asymmetric expansion of the hippocampal place field (Mehta et al., 2000), which can be accounted for by STDP of the excitatory connections in the hippocampal CA1 region (Abbott and Blum, 1996). This form of place field plasticity may underlie sequence learning during spatial navigation, which was in fact predicted in a theoretical study (Abbott and Blum, 1996) several years before experimental findings of STDP attracted wide attention. Since various types of motion are common in the natural environment, they are likely to constitute an important class of events that shape the neural circuits through STDP.

Computational Implications

Numerous theoretical studies have explored the functional implications of STDP. This synaptic learning rule has several distinct features: (1) the *bidirectionality* of synaptic modification with approximately balanced LTP and LTD, which helps the neural circuit to maintain its net synaptic excitation at a stable level, avoiding runaway excitation; (2) the *spike sequence dependence* of synaptic modification, which allows the circuit to learn sequences and to code causality of external events; (3) the *narrow temporal window*, which allows the system to select inputs based on its response latency with a millisecond precision, thus shaping the temporal dynamics of the circuit. Here, we will review a subset of theoretical studies that emphasize these three features. For more detailed reviews of theoretical studies of STDP, see the special issue of *Biological Cybernetics* [volume *87*(5–6), 2002].

Compared to the traditional correlation-based rule governing synaptic modification (Miller, 1994), the *bidirectionality* of STDP provides a mechanism for competition between converging inputs. Modeling studies showed that a critical requirement for competition is that the area under the LTD window must be larger than that under the LTP window (Song et al., 2000), which is observed at many synapses (e.g., Feldman, 2000), as this will ensure that uncorrelated pre/post spiking causes synaptic depression, leading to a stable distribution of synaptic strengths. At such distribution, the mean input to the neuron keeps the membrane potential near the firing threshold, so that postsynaptic spike timing becomes irregular, as that found in vivo (Softky and Koch, 1993; Shadlen and Newsome, 1994).

The *spike sequence dependence* of STDP allows neural circuits to learn temporal sequences and causal relationships between events in the external world and to predict future events based on previous stimuli (Abbott and Blum, 1996; Roberts, 1999). In general, the STDP learning rule corresponds closely to differential Hebbian learning (Roberts, 1999; Rao and Sejnowski, 2000), in which synaptic modification is proportional to the time derivatives of pre- and postsynaptic firing rates rather than the firing rates per se. Since the differential learning rule has been used successfully to account for classical conditioning at the behavioral level, STDP should allow similar learning of event association based on timing. Sequence/predictive learning can be manifested in various forms. For example, the asymmetric expansion of hippocampal place fields described above (Mehta et al., 2000) may mediate path learning and projection (Blum and Abbott, 1996). In a circuit with a range of latencies for the presynaptic inputs, transient inputs with short latencies tend to be strengthened by pre→post potentiation, and inputs with long latencies and sustained kinetics are likely to be eliminated by the post→pre depression, leading to reduced response latency of the postsynaptic cell. In conjunction with inhibitory connections (Rao and Sejnowski, 2000) or short-term synaptic depression (Buchs and Senn, 2002), STDP also allows development of direction selectivity in cortical neurons.

The *narrow temporal window* can directly affect the temporal response properties of the neural circuits. For example, in a model circuit for sound localization based on interaural time difference (ITD), an STDP window with a width of $\sim$1 ms allows the development of ITD tuning with submillisecond precision (Gerstner et al., 1996) and the formation of a temporal feature map (Kempter et al., 2001). Although such a narrow window has not been observed experimentally, the same principle should apply for shaping the temporal properties of neural circuits at longer time scales. In many circuits, STDP can facilitate synchronization between neurons (Suri and Sejnowski, 2002; Nowotny et al., 2003).

Concluding Remarks

Plasticity of neural circuits is essential for the development and integrative functions of the nervous system. The recognition of the importance of the temporal order of correlated pre- and postsynaptic spiking in causing persistent modifications of synaptic efficacy, neuronal excitability, and dendritic integration has brought new insights into the functional plasticity of neural circuits. Incorporation of these cellular changes into realistic circuit models will be an important step in understanding the neural basis of higher cognitive functions such as learning and memory.

Acknowledgments

This work is supported in part by grants from NIH (EY014887 to Y.D; NS 36999 to M.-m.P.).

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