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Spike Timing-Dependent Plasticity: From Synapse to Perception

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Dan, Yang, and Mu-Ming Poo. Spike Timing-Dependent Plasticity: From Synapse to Perception. *Physiol Rev* 86: 1033–1048, 2006; doi:10.1152/physrev.00030.2005.—Information in the nervous system may be carried by both the rate and timing of neuronal spikes. Recent findings of spike timing-dependent plasticity (STDP) have fueled the interest in the potential roles of spike timing in processing and storage of information in neural circuits. Induction of long-term potentiation (LTP) and long-term depression (LTD) in a variety of in vitro and in vivo systems has been shown to depend on the temporal order of pre- and postsynaptic spiking. Spike timing-dependent modification of neuronal excitability and dendritic integration was also observed. Such STDP at the synaptic and cellular level is likely to play important roles in activity-induced functional changes in neuronal receptive fields and human perception.

I. INTRODUCTION

Since the discovery of persistent enhancement of synaptic transmission by tetanic stimulation in the hippocampus (14), a phenomenon now generally referred to as long-term potentiation (LTP), the study of activity-dependent synaptic plasticity has become one of the most active areas in neurobiology (66, 68). Two features of LTP, the associativity and input specificity, match the properties of some forms of learning and memory, suggesting that LTP may underlie such 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) (53, 77). 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 (57) 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. Later studies have further addressed the importance of the temporal order of pre- and postsynaptic spiking in long-term modification of a variety of glutamatergic synapses and have defined the "critical windows" for spike timing (12, 13, 15, 24, 28, 31, 37, 65, 67, 97, 107, 119). As illustrated in Figure 1, when presynaptic spiking precedes postsynaptic spiking (hereafter referred to as "pre-post") within a window of several tens of milliseconds, LTP is induced, whereas spiking of the reverse order ("post-pre") leads to LTD. This form of activity-dependent LTP/LTD is now referred to as spike timing-dependent plasticity (STDP) (99). While the dependence of synaptic modification on the pre/post spike order is commonly observed, the width of the STDP window varies. In Table 1, we list the pre/post spike intervals at which LTP and LTD have been detected at different synapses. In addition to these glutamatergic synapses, a recent study of GABAergic synapses in rat hippocampal cultures and slices showed that repetitive postsynaptic spiking within 20 ms either before or after presynaptic activation led to a persistent change in the GABAergic synaptic strength (115), giving rise to a symmetric temporal window.

Beyond the initial characterization of the STDP windows, more recent experimental studies have addressed the following questions: What cellular mechanisms underlie the temporal windows for LTP/LTD? What are the rules determining the synaptic modification induced by complex spike patterns, including high-frequency bursts? How does STDP affect the operation of neural circuits and higher brain functions such as sensory perception? In addition to synaptic modification, is there STDP in neuronal excitability and dendritic integration? We here review findings pertinent to these questions.

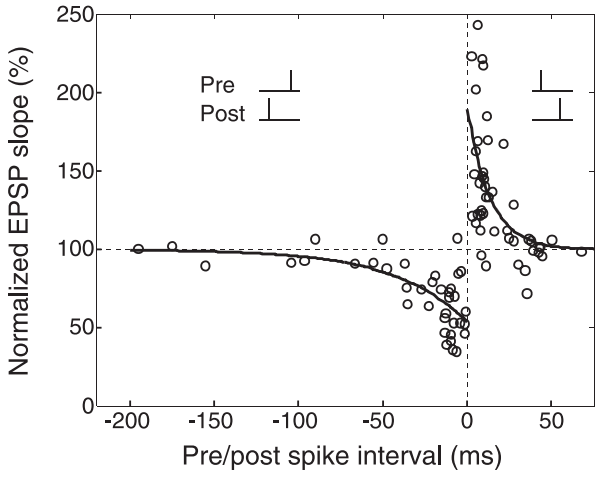

FIG. 1. Synaptic modification induced by repetitively paired pre- and postsynaptic spikes in layer 2/3 of visual cortical slices from the rat. Each symbol represents result from one experiment. Curves are single exponential, least-squares fits of the data. *Insets* depict the sequence of spiking in the pre- and postsynaptic neurons. EPSP, excitatory postsynaptic potential.

II. CELLULAR MECHANISMS UNDERLYING SYNAPTIC SPIKE TIMING-DEPENDENT PLASTICITY

In conventional protocols using steady postsynaptic depolarization, high-frequency presynaptic stimulation induces LTP and low-frequency stimulation induces LTD, but in STDP low-frequency stimulation can be used to induce both LTP and LTD. While in both types of protocols activation of *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (NMDARs) (e.g., Refs. 13, 24, 65, 67, 119) and elevation of postsynaptic Ca^{2+} level are required, the effectiveness of postsynaptic spiking and steady depolarization in achieving the required Ca^{2+} level is likely to be different. This may account for the higher efficiency of the spike-timing protocol in long-term modification of excitatory synapses in hippocampal cultures (13) and midbrain slices (60). The NMDARs are largely blocked by Mg^{2+} at hyperpolarized membrane potentials, but the block can be relieved by depolarization (69, 83), leading to the idea that the NMDAR serves as the coincidence detector for pre/post activity. For LTP and LTD induced by conventional protocols, different cascades of signaling events are set in motion by high- and low-level postsynaptic Ca^{2+} elevation, respectively (66). Does the conventional Ca^{2+}-based model of LTP/LTD also explain the temporally asymmetric STDP? One would expect that pre-post spiking leads to a brief high-level Ca^{2+} influx, due to effective activation of NMDARs by postsynaptic spiking, while post-pre spiking leads to a low-level Ca^{2+} rise due to the limited extent of NMDAR activation by the afterdepolarization associated with the postsynaptic action potential (AP). Fluorescence Ca^{2+} imaging studies indeed demonstrated that Ca^{2+} influx through NMDARs and voltage-dependent Ca^{2+} channels (VDCCs) exhibits supralinear summation with pre-post spiking and sublinear summation with post-pre spiking (56, 79). In support of this Ca^{2+} model for STDP, pre-post spiking under partial inactivation of NMDARs in CA1 hippocampus leads to the induction of LTD instead of LTP (81). However, such a simple model is unlikely to provide a complete explanation for the STDP window.

TABLE 1. *Temporal window for STDP of glutamatergic synapses*

Synapse	LTP Window, ms	LTD Window, ms	Reference Nos.
Rat (hippocampal slice) entorhinal cortex → dentate gyrus	0–20	<0	57
Electric fish (electrosensory lobe, slice) parallel fiber → Purkinje-like cell	<0 or >50	0–50	12
Xenopus tadpole (in vivo) retina → tectum	0–40	0 to −20	119
Zebra finch (brain slice) $LMAN_R$ → LMAN	0–15	0 to −7	15
Rat (hippocampal culture)	0–30	0 to −40	13, 58
Rat (hippocampal slice culture) CA3 → CA3	15	0 to −200	24
Rat (hippocampal slice) Schaffer collateral/commissural → CA1	0–10	−15 to −30 and 15–25	81
Rat (hippocampal slice) Schaffer collateral → CA1	3–10*		59
Rat (neocortical slice) L5 → L5	10	−10	67
Rat (barrel cortical slice) L4 → L4	NF	−10 to 25	28
Rat (barrel cortical slice) L4 → L2/3	0–15	0 to −100	31
Rat (visual cortical slice) L5 → L5	10	0 to −50	97
Rat (visual cortical slice) input to L2/3; proximal (A), distal (B)	0–25 (A) 0–25 (B)	0 to −50 (A) 0 to −100 (B)	38
Mouse (brain stem slice) parallel fiber → fusiform (A), cartwheel (B)	5–10 (A) NF (B)	−5 (A) 5 (B)	107

Due to the sparsity of data points in some studies, the listed range of intervals may not reflect the full width of the window. For window data: positive interval, pre-post; negative interval, post-pre. NF, not found. * Activation of β-adrenergic receptors broadens this window to 3–15 ms.

A. LTP Window

The ~20 ms pre-post window for LTP induction is much shorter than the time constant for the dissociation of glutamate from NMDARs (109). One explanation of this narrow LTP window is the kinetics of Mg^{2+} unblock of the NMDARs. Using nucleated patches of neocortical pyramidal neurons, Kampa et al. (50) measured the rate of depolarization-induced Mg^{2+} unblock of NMDARs at different times after a brief pulse of glutamate application. They found that Mg^{2+} unblock consists of a fast and a slow component, whose relative amplitudes depend on the timing of the depolarization relative to the glutamate pulse, with the fast component preferentially reduced at later times. Thus the postsynaptic spikes arriving immediately after glutamate binding are more effective in opening NMDARs, thus sharpening the time window for LTP induction. In addition to the property of NMDARs, postsynaptic cytoplasmic processes, including Ca^{2+}-dependent Ca^{2+} release from internal stores and activation of downstream effectors, both of which are likely to be highly nonlinear, may further boost the effect of the earlier arriving postsynaptic APs and sharpen the LTP window. The importance of cytoplasmic processes is further supported by the finding that activation of β-adrenergic receptors can increase the width (but not the magnitude) of the LTP window at Schaffer collateral-CA1 pyramidal cell synapses (59), an effect that depends on protein kinase A or mitogen-activated protein kinase. Neuromodulatory inputs may also affect the STDP window by modifying the AP profile through the modulation of the density and properties of axonal and dendritic ion channels, such as transient (I_A) and Ca^{2+}-activated (BK and SK) K^+ channels (95, 112).

B. LTD Window

The simplest explanation for the post-pre LTD window is that the afterdepolarization associated with the AP causes a partial opening of NMDARs, resulting in a low-level Ca^{2+} influx required for LTD induction. However, such a simple model inevitably predicts the existence of a LTD window at positive (pre-post) intervals longer than those for LTP induction. This is because, as the amount of Ca^{2+} influx through NMDARs decreases with the pre-post interval, it must pass through the range appropriate for LTD induction before reaching the baseline. Although such a pre-post LTD window has been found in hippocampal slices (81), it was not reported in any other study. A potential resolution of this paradox is that excitatory postsynaptic potentials (EPSPs) in the absence of postsynaptic AP may already induce Ca^{2+} elevation above that required for LTD induction (but insufficient to induce LTP); thus pre-post spiking can only lead to LTP. For post-pre spiking, other mechanisms such as spiking-induced afterhyperpolarization or NMDAR desensitization (88, 106, 108) reduce the Ca^{2+} influx through NMDARs to a level appropriate for LTD induction (38). Alternatively, a second coincidence detector independent of NMDAR is responsible for LTD at post-pre intervals. Karmarkar and Buonomano (51) suggest that the mGluR pathway, which is coupled to Ca^{2+} influx through VDCCs, is a likely candidate for this second coincidence detector. This model is consistent with the finding of a mGluR-dependent form of homosynaptic LTD in the hippocampus induced by both low-frequency stimulation (47, 84) and post-pre spiking (82). Furthermore, postsynaptic spiking-triggered secretion of retrograde factors, e.g., endocannabinoids, may act together with the activation of presyn-

aptic NMDARs to induce LTD (96), as blocking the degradation of endocannabinoids was found to widen the LTD window. Besides Ca^{2+} influx through NMDARs, activation of L-type VDCCs by postsynaptic spiking (13) and Ca^{2+} release from internal stores (81) are also shown to be necessary for spike-timing dependent LTD. Because Ca^{2+} from these sources and through NMDARs may have different spatiotemporal profiles, they may play different roles in the induction of synaptic modifications.

C. Modulation of STDP by Inhibitory Inputs

Because both feed-forward 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 profoundly influence the induction of LTP/LTD (113). During development, the Schaffer collateral input to CA1 pyramidal neurons becomes progressively less susceptible to LTP induction by pre/post spike pairing (74), and postsynaptic spike bursts are necessary in adult animals to induce LTP. This developmental reduction in the effectiveness of spike pairing for LTP induction can be reversed by blocking $GABA_A$ receptor-mediated inhibition. Similar GABA-mediated "gating" of LTP is also found at excitatory inputs to dopamine neurons in the ventral tegmental area (VTA) of the rat midbrain (60). Interestingly, repeated exposure of the rat to cocaine in vivo leads to a reduction of GABAergic inhibition, allowing LTP induction by the spike pairing protocol in acute midbrain slices, while enhancing GABAergic transmission in the slices from cocaine-treated animal with diazepam eliminated LTP induction. By titrating the strength of GABAergic inputs with different doses of a $GABA_A$ antagonist, Liu et al. (60) concluded that a 30% reduction of GABAergic transmission in normal rat VTA can open the gate for LTP induction. Finally, there is evidence that the LTD window at positive timing found in hippocampal slices (81) may be due to feedforward inhibition in the circuit (104).

III. SPIKE TIMING-DEPENDENT PLASTICITY WITH COMPLEX SPATIOTEMPORAL ACTIVITY PATTERNS

A. Dependence on Dendritic Location

A prominent morphological feature of the neuron is its extensive dendritic tree, where most of the synapses are located. Due to cable filtering and the nonuniform distribution of voltage-dependent ion channels (49), neuronal processing of each synaptic input depends strongly on its dendritic location (44, 94). Because STDP involves the interaction between the synaptic input and the back-propagating AP as well as the downstream cellular mechanisms highly localized at the synaptic site, it is likely to be dendritic location dependent. Indeed, both the amplitude and width of the STDP window were found to vary along the apical dendrite of the pyramidal neuron in layer 2/3 (L2/3) of visual cortical slices (38). At the intermediate-distal portion of the dendrite (100–150 μm from soma), the magnitude of LTP is smaller and the temporal window for LTD is broader than at the proximal dendrite. The smaller magnitude of LTP may be related to the attenuation of the back-propagating AP at the distal dendrite. The LTD window, on the other hand, was found to correlate with the window for the suppression of NMDA receptor-mediated EPSPs by the back-propagating APs, both across dendritic locations and under various pharmacological manipulations. This is consistent with the notion that the AP-induced suppression of EPSPs plays an important role in LTD induction, and the variability in the LTD window among different synapses may be attributed in part to differences in the dendritic location of the synapse.

Functionally, the dendritic inhomogeneity of the STDP window may allow differential selection of synaptic inputs at different portions of the dendrites according to the temporal characteristics of the presynaptic spike trains, as suggested by simulation studies (38). Although spatial inhomogeneity in the electrical properties and nonlinearity in dendritic integration are thought to endow individual pyramidal neurons with enhanced processing capacity (44, 94), the computational power can only be harvested if the inputs carrying different signals are segregated into distinct regions (8, 72). In fact, the importance of domain-specific inputs has been well recognized for inhibitory interneurons (35, 54, 86). The function and mechanism of the dendritic segregation of excitatory inputs remain largely unexplored.

While differences in the amplitude and width of the STDP window have been observed from the proximal to the intermediate segment of the apical dendrite, other differences may exist in the more distal region. For example, in some neurons, the back-propagating APs may not reach the distal tip of the dendrite, which will preclude the EPSP-AP interaction required for STDP induction. Instead, LTP may be induced by other mechanisms such as the local Ca^{2+} spikes resulting from strong synaptic inputs (43). Furthermore, while studied much less extensively than the main trunk of the apical dendrite due to technical difficulties, the basal and oblique dendrites of pyramidal neurons in fact receive most of the synaptic inputs (85). How STDP and other forms of synaptic modification operate on these dendrites remain to be investigated.

B. Complex Spike Trains

In most in vitro studies of STDP, the induction protocol consists of relatively simple spike patterns with pre/post spikes paired at regular intervals. The advantage of this approach is that each induction pattern can be described by a small number of parameters, and the dependence of synaptic modification on these parameters (e.g., pre/post spike interval) can be easily determined. For neural circuits in vivo, however, spiking in both pre- and postsynaptic cells is likely to be irregular (98), with occasional high-frequency bursts. How well does the STDP window (Fig. 1) account for the effects of complex spike trains? Do all the pre/post spike pairs contribute independently to long-term synaptic modification?

This question was addressed in L2/3 of visual cortical slices by progressively increasing the complexity of the induction pattern (37). First, a single spike, either pre- or postsynaptic, was added to the spike pair to form a "triplet," which consists of two pre/post pairs. By measuring synaptic modification at various intervals, the first spike pair was found to play a dominant role in determining the sign and magnitude of synaptic modification. Based on this observation, a simple phenomenological model was proposed in which the efficacy of each spike in synaptic modification is suppressed by the preceding spike in the same neuron in a time-dependent manner, and the contribution of each spike pair in synaptic modification is scaled by the efficacies of both spikes. Compared with the default "independent model," the suppression model significantly improved the prediction of synaptic modification induced by more complex spike patterns, including spike quadruplets and spike train segments recorded in vivo in response to natural stimuli. Interestingly, such suppressive interaction between neighboring spikes 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 (52).

The effects of complex spike trains in LTP/LTD induction were also examined in L5 of visual cortical slices, using paired bursts of spikes with varying pre/post intervals and burst frequencies (97). In addition to the pre/post interval, synaptic modification was also found to depend on the firing frequency within each burst in a manner that cannot be accounted for by the STDP window. The magnitude of LTP, but not LTD, increases with the burst frequency (67, 97), and at high frequencies LTP was observed regardless of the pre/post interval (97). This finding suggests that LTP induced by pre-post pairs "wins over" LTD induced by post-pre pairs, and a model implementing this "LTP dominant" rule indeed improved the prediction of the effects of Poisson spike trains in synaptic modification. Alternatively, since with high-frequency bursts synaptic modification is no longer sensitive to the timing of individual spikes, perhaps a burst of spikes should be considered collectively as a basic unit in synaptic modification. Consistent with this idea, a recent study in the CA3 region of the hippocampus (55) 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 order and interval between the pre/post bursts rather than between individual spikes.

For a synaptic learning rule used to understand computation at the circuit level, the disadvantage of treating each burst as a distinct unit is that separate rules must be characterized for these bursts. It is unclear how many types of bursts one must consider, with varying numbers of spikes and burst frequencies, and whether each type warrants a different rule. In an attempt to "rescue" the learning rule based on the timing of individual spikes, Froemke et al. (39) systematically varied the frequency, timing, and number of spikes in both the pre- and postsynaptic bursts to identify the situations under which the suppression model (37) breaks down. Consistent with the finding of Sjostrom et al. (97) in L5 synapses, L2/3 synapses also exhibit a frequency-dependent transition from LTD to LTP induced by a postsynaptic burst (5 spikes) preceding a presynaptic burst. However, this frequency dependence is a natural consequence of timing-dependent interactions among individual spikes in the paired bursts, and a simple modification of the original suppression model (37) can account for synaptic modifications induced by a variety of spike trains. Furthermore, pharmacological experiments suggest that short-term depression of presynaptic transmitter release and the kinetics of postsynaptic APs during a burst play important roles in the suppressive interactions among multiple spikes in the induction of long-term synaptic modification.

The suppression rule described above for cortical slices, however, does not seem to apply to cultured hippocampal synapses. Wang et al. (110) found that pre-post-pre triplets induce little synaptic modification, whereas post-pre-post triplets induce significant LTP. Thus the effect of the first pair appears to be "vetoed" by the second pair, opposite to that described by the suppression model (37). Given the similarity in the induction protocol, the discrepancy between the findings in cortical slice and hippocampal culture may be attributed to the different properties of synapses in these circuits, such as short-term synaptic plasticity, kinetics of postsynaptic APs, or downstream intracellular mechanisms leading to LTP and LTD. Pharmacological experiments by Wang et al. (110) suggest that the Ca^{2+}/calmodulin kinase II (CaMKII)-mediated potentiation process and a calcineurin-mediated depression process are both activated by the triplets, and they interact in a nonlinear manner.

Finally, in addition to interspike interactions at the time scale of tens of milliseconds, there are also interactions at longer time scales in STDP induction. For example, the amount and persistence of synaptic modification may depend on the temporal distribution of the spiking activity. While synaptic modification may saturate within a single induction episode, a resting period of minutes to hours 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 (122), a phenomenon reminiscent of the differential effects of "mass" versus "spaced" learning (see below). The susceptibility of the synapse to modification may also depend on the state of the synapse, which can be a function of both the current synaptic strength (13, 23, 110) and the prior history of modification (75). Further clarification of these issues is important for understanding the functional roles of STDP in vivo.

In summary, a universally applicable model for predicting synaptic modification induced by complex spike trains must incorporate all the cellular events involved in the induction of LTP and LTD. Of particular importance is the spatiotemporal pattern of Ca^{2+} elevation that is regulated by a variety of factors. On the other hand, elucidation of simple and analytically tractable phenomenological rules is useful for exploring the functional implications of synaptic plasticity in large neuronal circuits, even in the absence of a complete understanding of the cellular mechanisms.

IV. SPIKE TIMING-DEPENDENT PLASTICITY IN VIVO

While most of the earlier studies focused on characterizing STDP at identified synapses in slices or cell cultures, more recent studies have begun to address the functional consequences of STDP in vivo. These studies are briefly summarized in Table 2. For more detailed descriptions of these studies, we have divided them into three groups, based on how spike timing is controlled experimentally to induce circuit modifications. First, postsynaptic spiking is evoked by electrical stimulation, while presynaptic activation is induced by either sensory or electrical stimulation. Second, neuronal spike timing is manipulated by pure sensory stimuli. Third, natural patterns of sensory stimuli are applied, but the resulting changes in the circuit functions are thought to involve STDP.

A. Electrical Stimulation

The first in vivo study of STDP was carried out in the developing *Xenopus* retinotectal circuit. Using whole cell recordings from the tectal neurons to monitor the synaptic inputs from retinal ganglion cells, Zhang et al. (119) found that these synapses undergo STDP with temporally asymmetric time windows, similar to those found in hippocampal cultures (13). The demonstration of STDP in this circuit in vivo has important implications in the developmental refinement of the retinotectal projection: a strong input that can elicit spiking by itself should have a competitive advantage among converging inputs, because the onset of its EPSPs relative to the postsynaptic spiking is always within the potentiation window. For a weak input not sufficient to evoke postsynaptic spiking on its own, however, the timing of its activation relative to other inputs becomes critical in determining its fate: activation within a 20-ms window before postsynaptic spiking initiated by other inputs leads to potentiation, whereas activation shortly after spiking leads to depression and perhaps the eventual elimination of the input.

The functional consequence of STDP has also been examined in the mammalian visual system. In the kitten visual cortex (92), repetitive pairing of a brief oriented visual stimulus with electrical stimulation of the cortex for 2–4 h induced substantial, long-lasting reorganization of the orientation map, as revealed by intrinsic optical imaging. At the site of stimulation, the cortical response to the paired orientation was enhanced or depressed, when the cortex was activated visually before or after the electrical stimulation by 10–20 ms, respectively, consis-

TABLE 2. *STDP of circuit functions in vivo*

Species and Circuits	Stimuli (Pre/Post)	Modification	Reference Nos.
Xenopus retinotectal system	Electrical stimulation/intracellular current injection	Synaptic response	119
Rat visual cortex	Visual stimulation/intracellular current injection	Spatiotemporal receptive field	73
Rat barrel cortex	Whisker deprivation	Synaptic response	5, 18
Rat hippocampus	Exploratory movement	Place field position	71
Kitten visual cortex	Visual stimulation/intracortical stimulation	Orientation tuning	92
Cat visual cortex	Visual stimulation/visual stimulation	Receptive field position	40, 117, 118
Cat visual cortex	Motion stimuli	Receptive field position	41
Human motor cortex	Somatosensory stimulation/TMS stimulation	TMS response	101, 114

tent with STDP of intracortical connections. In parallel with optical imaging, single-unit recordings showed that pairing at the positive interval (visual before electrical) caused an ~20° shift in the preferred orientation of the neurons toward the paired orientation. In the developing rat visual cortex, whole cell recordings showed that synaptic responses evoked by a flashed bar can be modified by pairing the bar stimulus with postsynaptic spiking elicited by the whole cell electrode (73). The direction of the modification depends on the temporal order of the synaptic response and the postsynaptic spiking in a manner consistent with STDP found in visual cortical slices (37). Note that, while earlier studies using extracellular K^+ or pharmacological agents (33, 34) to stimulate the cortical neurons demonstrated the role of coincidence between sensory stimuli and cortical activation in receptive field (RF) modification, the two recent studies described above provided more precise control of cortical spike timing at the millisecond level, thus revealing the importance of the order of visual and cortical activation in RF modification.

Remarkably, plasticity resembling STDP has been demonstrated in the human motor cortex (101, 114). The induction protocol, termed paired associative stimulation (PAS), consists of repetitive pairing of median nerve stimulation (which activates somatosensory inputs to the primary motor cortex) with transcranial magnetic stimulation (TMS) of the motor cortex. Response to the TMS stimulation, measured by electromyographic (EMG) activity of the corresponding muscle, was found to be potentiated or depressed by 90 pairs of PAS, depending on whether the somatosensory input arrived before or after motor cortical activation by TMS, consistent with the time window of STDP. The potentiation is blocked by the NMDAR antagonist dextromethorphan, and the depression is blocked by both dextromethorphan and nimodipine, a blocker of L-type VDCCs, identical to the pharmacological properties of STDP in hippocampal and cortical synapses (see above).

B. Sensory Stimulation

In several other studies, spiking of cortical neurons was evoked by visual stimulation in the absence of electrical stimulation, allowing a more physiological condition for studying the functional significance of STDP. In adult cat V1, pairing of visual stimuli at two orientations for several minutes induced a shift in the orientation tuning of cortical neurons, with the direction of the shift depending on the temporal order of the stimulus pair (117). The induction of significant shift required that the interval between the pair fall within ±40 ms, reminiscent of the temporal window for visual cortical STDP (37). This RF modification is likely to occur at the cortical level rather than in the earlier visual circuits, such as the retina or the lateral geniculate nucleus, because the shifts induced by monocular conditioning exhibit complete interocular transfer, indicating that the underlying circuit changes occur after signals from the two eyes converge. In addition, a model circuit with STDP implemented at the intracortical connections can account for both the temporal and orientation specificity of the effect (118).

With the assumption that the responses of these orientation-selective cortical neurons underlie the perception of stimulus orientation, a change in the neuronal tuning in one direction should lead to a shift in perceived orientation in the opposite direction. This prediction was tested in human psychophysical experiments using the conditioning stimuli similar to those in the electrophysiology experiments and a two alternative forced-choice task to measure perceived orientation before and after conditioning. Significant perceptual shifts were induced when the interval between the pair of stimuli was within ±40 ms, similar to the window measured for cat cortical neurons (117). Furthermore, the perceptual shift induced by monocular conditioning showed complete interocular transfer, indicating that the change is cortical in origin (118).

In addition to the orientation domain, stimulus-timing-dependent cortical modification has also been demonstrated in the space domain (40). 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 (revealed by cross-correlation analysis) and shifts of the RF center (Fig. 2). These changes depended on the temporal order and interval between the pair of 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. The similarity in the temporal window of stimulus-induced cortical modifications at multiple levels, from synapse to perception, strongly suggests that STDP and the asynchronous stimulus-induced functional changes in the visual cortex are causally related.

C. Natural Stimuli

To gain further insights into the functional implications of STDP, it is important to examine the effects of natural sensory stimuli. Of particular interest are the moving stimuli commonly found in natural scenes, since they can activate neighboring V1 neurons at short temporal intervals, thus modifying their synaptic connections through STDP. The interaction between motion stimuli

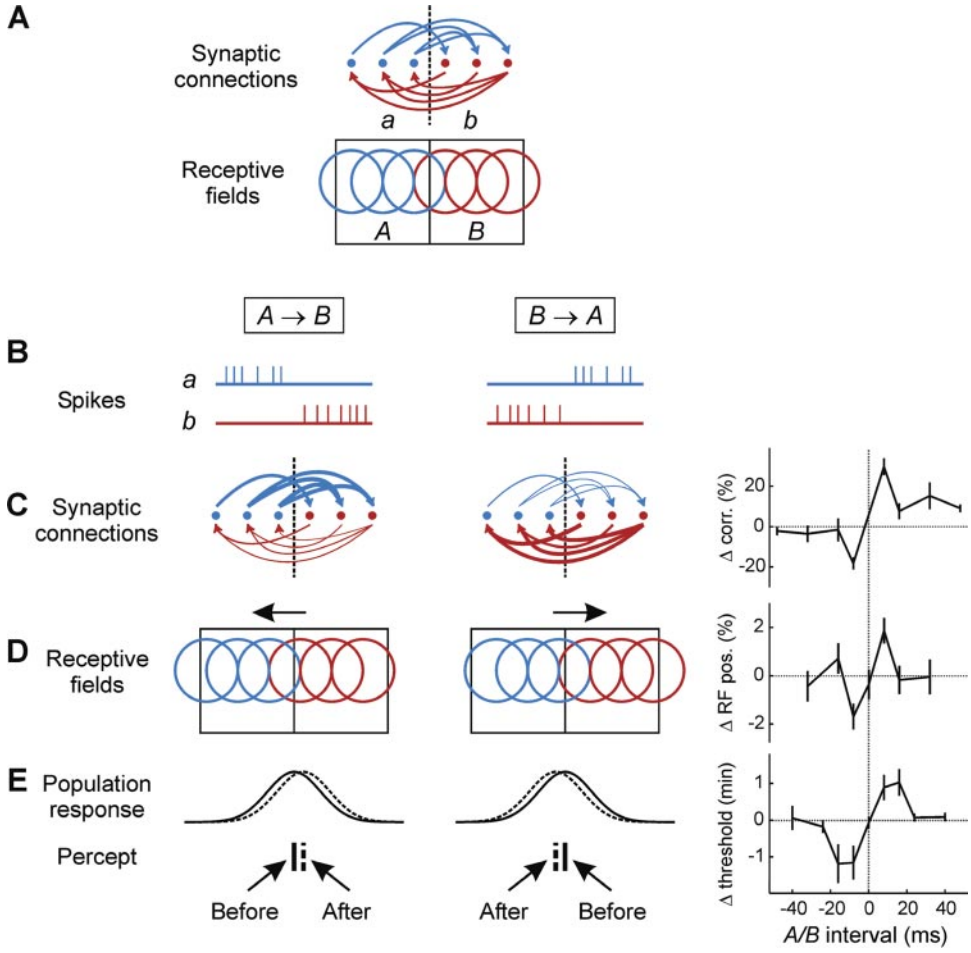

FIG. 2. A model for stimulus timing-dependent visual cortical modification. *A*: intracortical excitatory connections between two groups of neurons, *a* and *b*, whose receptive fields (RFs) fall in regions *A* and *B*, respectively. *B*: schematic illustration of neuronal spike timing in response to *A*→*B* and *B*→*A* stimulation. *C*: connection weight (represented by line thickness) after visual conditioning. *Right plot*, change in intracortical connection (from cross-correlation analysis) versus *A*/*B* interval measured in cat V1. *D*: RFs after conditioning. Arrow indicates predicted direction of shift. *Right plot*, RF shift measured in cat V1. *E*, *top*: spatial profiles of population responses evoked by a stimulus at *A*/*B* border before (solid curve) and after (dashed curve) conditioning. *Bottom*: perceived stimulus positions predicted by the model. *Right plot*, average perceptual shift measured in four human subjects. [Adapted from Fu et al. (40).]

and STDP in shaping the visual cortical function has been explored in a simple model circuit, which consists of a postsynaptic neuron ("target neuron") and two sets of direction-selective presynaptic neurons preferring either left- or rightward motion (Fig. 3). A rightward moving object should evoke a wave of spiking preferentially from the neurons preferring rightward motion ("→ neurons", red circles in Fig. 3), with the neurons on the left side of the retinotopic map firing before the target neuron, and those on the right firing afterwards. According to STDP,

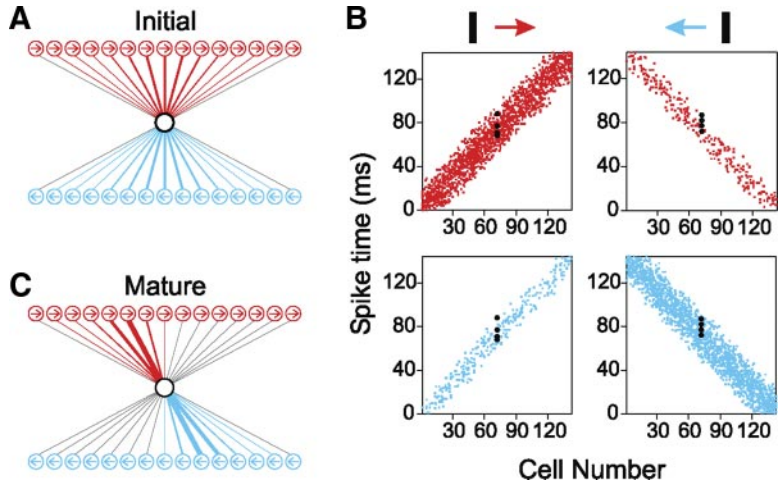

FIG. 3. Development of asymmetric visual cortical circuit through spike timing-dependent plasticity (STDP). *A*: initial circuit with symmetric connections. Arrow in each circle represents direction selectivity of the cell. Line thickness represents synaptic strength (the weakest connections are shown in gray). *B*: simulated spatiotemporal spike patterns in the circuit evoked by a small object (*top*) moving rightward (*left column*) or leftward (*right column*) across the visual field. Each red or blue dot represents a spike of a presynaptic neuron (indexed 1 to 143, from *left* to *right*) with the corresponding color. Black dots represent spikes of the target neuron. *C*: mature circuit after extensive exposure to motion stimuli in both directions, during which the connections underwent spike timing-dependent modification.

the connections from the → neurons on the left should be potentiated, and those from the right should be depressed, causing a leftward bias in the intracortical connections from these → neurons. For the same reason, a leftward moving object should cause a rightward bias in the connections from the → neurons. Thus, although in the natural environment right- and leftward motion stimuli are equally common, the above process operating during circuit development should lead to an asymmetry in the intracortical connections from direction-selective cells in the adult visual cortex. This asymmetry predicts two novel effects of motion stimuli on RF position. First, motion signals in stationary test stimuli should cause a displacement of the RF in the direction opposite to motion. Second, adaptation to motion stimuli should induce a shift of the RF in the direction of adaptation. Both predictions have been confirmed experimentally in adult cat visual cortex (41). Furthermore, comparison between these effects observed in cat V1 and human psychophysical measurements indicate that these RF properties can largely account for two previously known motion-related illusions.

The notion that during early development motion signals can shape the direction-selective response properties of visual neurons was tested by examining the effect of moving bar stimuli on the visual responses of developing tectal neurons. Engart et al. (30) showed that exposure of *Xenopus* tadpole to repetitive unidirectional moving bar stimuli resulted in a rapid modification of the tectal circuit so that the response of the tectal neuron to the moving bar was selectively enhanced at the conditioned direction. This modification was persistent after conditioning and involved NMDAR-dependent potentiation and depression of different subpopulations of retinotectal connections (122). By repetitively pairing light bar stimuli with the spiking of the tectal neuron, Mu et al. (76a) found that the magnitude and polarity of the changes in the light-evoked excitatory synaptic responses in tectal neurons exhibited a temporal specificity consistent with STDP shown in Figure 1. Furthermore, spike timing-dependent LTP and LTD of the retinotectal synapses have been shown to require BDNF and nitric oxide (NO) signaling, respectively, and the direction-selective enhancement of tectal responses induced by the moving bar stimuli was abolished by the inhibitor of trkB signaling and NO synthesis (76a). These findings all support the idea that STDP mediates experience-dependent circuit refinement in the developing neural circuits.

In addition to 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 (71), which can be accounted for by STDP of the hippocampal CA3-CA1 connections (1). This form of place field plasticity may underlie sequence learning during spatial navigation, which was predicted in a theoretical study (1). Because 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.

Finally, experience-dependent plasticity of the somatosensory cortical map may also involve STDP. Using a linear electrode array to record simultaneously from L4 and L2/3 neurons in the same cortical column, Celikel et al. (18) found that trimming the principle whisker corresponding to the recorded cortical column, such that it escapes the stimulation applied simultaneously to all whiskers, causes an immediate reversal of the order of spiking of L4 and L2/3 neurons, with only modest effects on the firing rate. According to the STDP window for these L4-L2/3 synapses measured in slices (31), the relative spike timing of L4 and L2/3 neurons during normal multiwhisker stimulation should cause little synaptic modification, while the whisker trimming-induced change in spike timing should cause significant LTD of the L4-L2/3 synapses. Indeed, depression of L4-L2/3 synaptic transmission has been demonstrated in barrel cortical slices from animals with whisker deprivation (5), and such trimming-induced depression occluded further LTD and enhanced LTP of these synapses in slices. These results suggest that STDP is also involved in the developmental cortical modifications induced by sensory deprivation.

D. Persistence of STDP In Vivo

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 freely moving adult rats showed that electrically induced LTP in the hippocampus is quickly reversed when the rat enters a novel environment within 1 h after induction (116). 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 of the tectal neuron or by random visual stimuli (122). 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 spontaneous activity in vivo may account for the short-term nature of STDP of cortical RFs and human visual perception (40, 117). In the retinotectal system, the reversal of LTP can be prevented by repeating the induction protocol a few times at an optimal spacing (122). Such a requirement for "spaced" induction protocol may prevent accidental pairing of pre/post spikes from causing lasting changes in the neural circuits.

The cellular mechanism underlying the reversal of LTP by spontaneous activity in vivo may be similar to that underlying the homosynaptic "de-potentiation" in hippocampal slices, in which low-frequency stimulation of the same pathway within tens of minutes following LTP induction protocol causes the reversal of LTP. In both cases the LTP reversal depends on the activity of protein phosphatases (see review in Ref. 121).

V. NONSYNAPTIC ASPECTS OF SPIKE TIMING-DEPENDENT PLASTICITY

A. STDP of Intrinsic Neuronal Excitability

Persistent changes in neuronal excitability following repetitive activity have long been noted in the studies of associative learning in various systems (see reviews in Refs. 21, 120). Changes in postsynaptic neuronal firing characteristics can result from modulation of either the excitatory/inhibitory synaptic drive or the intrinsic membrane conductances (intrinsic excitability). The latter has been reported in many systems. For example, activity associated with trace eye-blink 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 postburst afterhyperpolarization (76). In cerebellar deep nuclei, which are implicated in the trace eye-blink conditioning, brief high-frequency activation of mossy fiber inputs also causes a rapid and persistent increase in the intrinsic excitability (4). Similarly, theta burst stimulation (TBS) of mossy fibers potentiates 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 (9). Interestingly, although these changes in intrinsic excitability depend on NMDAR activation, they can occur in the absence of LTP, suggesting separate downstream mechanisms. The immediate changes of intrinsic excitability in all these studies point to the existence of rapid cytoplasmic signaling mechanisms that cause global modulation of ion channels in the neuronal membrane.

A form of spike timing-dependent modification of intrinsic neuronal excitability was also reported in hippocampal cultures, where the induction of LTP/LTD by correlated pre/post spiking is accompanied by an immediate and persistent enhancement/reduction of the intrinsic excitability of the presynaptic neuron, as reflected in a shift of the firing threshold and in the increased/decreased firing rate evoked by a constant depolarizing current injection at the soma (42, 58). This modification of excitability is temporally specific, with a requirement for pre/post spiking intervals identical to that for LTP/LTD (see Fig. 4). Similar to LTP/LTD induction, changes in the presynaptic excitability require activation of NMDARs and postsynaptic influx of Ca^{2+}, indicating that transsynaptic retrograde signaling is required. While presynaptic loading of PKC inhibitor (calphostin C or Ro-31–8220) through the whole cell pipette eliminated the spiking-induced increase in excitability, it only caused slight reduction of LTP. Thus, although the increased presynaptic excitability may contribute to LTP, it is not the primary cause (see below). Direct voltage-clamp measurements of Na^+ currents at the soma further showed that the increased excitability associated with LTP is related to changes in Na^+ channel activation and inactivation kinetics in favor of spike initiation. In the case of LTD, similar pharmacological and voltage-clamp studies showed that the reduction in excitability is related to an enhancement of the activation of slow-inactivating K^+ channels and that the activity of both protein kinase C (PKC) and protein kinase A (PKA) is required. Given the rapidity of these presynaptic changes (on the order of minutes) and the requirement for presynaptic PKA/PKC activities, post-translational modification of Na^+ and K^+ channels is the most likely underlying mechanism. Because the excitability measurements were carried out at the soma, it remains unclear to what extent the excitability is modified at the nerve terminal membrane, where changes in Na^+ and K^+ channel kinetics can affect the initiation and time course of the AP, which can in turn modulate evoked transmitter release and thus contribute to activity-induced changes in synaptic transmission.

In cell cultures, each presynaptic neuron makes many more synapses with the postsynaptic cell than that

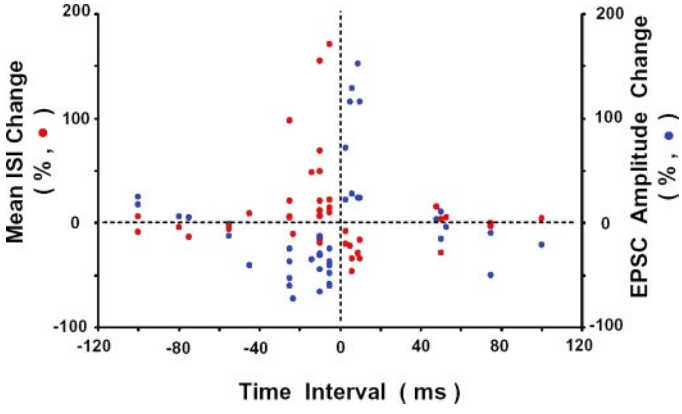

FIG. 4. Change in presynaptic excitability, measured by interspike interval (ISI) during depolarizing current injection, following the pre/post-spike pairing protocol in hippocampal culture. Each data point represents result from one experiment. The percentage changes for ISI (red) and excitatory postsynaptic current (EPSC) amplitude (blue) were calculated from the mean value at 10–20 min after correlated activation, compared with the mean value during the control period. The interval refers to the time between the onset of the excitatory postsynaptic potential and the peak of the postsynaptic spike.

in vivo, due to the artificial spatial proximity of the pre- and postsynaptic cells. Thus it is of interest to note that such global presynaptic modification was also observed in brain slices. Increased global excitability of the presynaptic cell was observed in L2/3 interneuron-pyramidal cell synapses in somatosensory cortical slices following the induction of spike timing-dependent LTD (58). Whole cell recording from cell pairs in which the presynaptic cell is a projection neuron with a long axon is much more difficult to achieve. It is possible that, in the latter situation, the retrograde influence due to LTP/LTD induction at the axonal terminal will be spatially more restricted, and global changes in excitability may not be detectable at the soma of the presynaptic cell.

B. STDP of Local Dendritic Excitability and Synaptic Integration

In addition to changes in the global presynaptic excitability, correlated activity also results in the modification of local postsynaptic excitability. In the original study of Bliss and Lomo (14), induction of LTP by tetanic stimulation was followed by an increase in the coupling between EPSPs and postsynaptic spiking ("E-S potentiation") that is distinct from the enhanced synaptic transmission (see Refs. 6, 20, 87). A reduction of the tonic inhibitory drive may contribute to E-S potentiation following LTP induction (3, 19, 61, 105), but local modification of dendritic conductances is also implicated (10, 45, 48). Recent dendritic 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 (36). In addition to LTP-associated changes, Daoudal et al. (22) found that LTD is also accompanied by an NMDAR-dependent, persistent E-S depression. This effect is input specific and is expressed when GABA receptors are blocked, suggesting a reduction in the intrinsic excitability of postsynaptic dendrites. In general, modulation of local active conductances depends on NMDAR activation and may represent a direct consequence of LTP/LTD induction. Local postsynaptic modulation of transmitter receptors, including their state of phosphorylation and the trafficking in and out of the subsynaptic membrane, have been implicated in LTP/LTD (11). Local modulation of voltage-dependent ion channels may be mediated by similar mechanisms.

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 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 (111). 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 attributed primarily to a local modification of I_h channels, which are known to influence dendritic summation of EPSPs (17, 63, 64). These changes in linearity accompanying LTP/LTD help to boost the effects of synaptic modification by further enhancing/reducing the contribution of the modified input to the firing of the postsynaptic neuron.

VI. SPREAD OF SYNAPTIC SPIKE TIMING-DEPENDENT PLASTICITY IN NEURAL CIRCUITS

A. Heterosynaptic Effects of LTP/LTD Induction

Activity-induced synaptic modifications are often thought to be input specific, i.e., only the synapses experiencing repetitive synaptic activation are modified (7, 26, 62, 80). However, there is also substantial evidence for two forms of "breakdown" of input specificity. First, the induction of LTP or LTD at one input to the postsynaptic cell may cause opposite changes in the synaptic efficacy of other adjacent inputs to the same cell. A typical example is the heterosynaptic LTD found in the CA1 region of the hippocampus following the induction of LTP (2, 16, 27, 62, 90). A similar heterosynaptic effect also occurs in the amygdala (89) and the cortex (46). The second form of breakdown is related to the heterosynaptic effects of the same polarity following LTP/LTD induction, leading to a spread of potentiation/depression to adjacent synapses. In hippocampal CA1 pyramidal cells, LTP induced by pairing pyramidal cell depolarization with stimulation of the Schaffer collateral inputs was found to spread to synapses made by Schaffer collaterals on neighboring pyramidal cells (93). In the same cells, LTD induced by low-frequency Schaffer collateral stimulation (100) or by correlated post-pre spiking (81) also spreads to other inputs to the same cell or reverse LTP previously induced in a separate pathway (78). In the CA1 region of the hippocampus, induction of LTD of excitatory synapses onto GABAergic interneurons by tetanic stimulation of the input fibers leads to a spread of depression to the neighboring excitatory synapses onto the same interneuron (70).

Using an elegant local perfusion method that restricted synaptic activation to a small region (<20 μm) of the hippocampal slice culture, Engert and Bonhoeffer (29) have estimated the extent of spread of LTP in the CA1 pyramidal cell. They found that LTP induced at one

Schaffer collateral input to the pyramidal cell by high-frequency stimulation could spread to other synapses onto the same pyramidal cell when the unstimulated inputs were within ~70 μm from the site of LTP induction. The mechanism underlying this lateral spread of LTP remains unclear. It may be mediated by cytoplasmic signals in the postsynaptic cell or by membrane-permeant diffusible factors that spread through the extracellular space. Given the finding that LTP induced at one pyramidal cell can spread to synapses on adjacent pyramidal cells (93), it appears that local extracellular signals are involved in spreading the potentiation. The localized nature of these signals is also consistent with earlier findings of input specificity of LTP, where unstimulated control inputs were usually chosen to be relatively far from the stimulated input.

B. Spread of LTP/LTD in Cell Culture

Understanding the rules governing the nonlocal effects of LTP/LTD is essential for a full understanding of activity-induced modifications of neural circuits. Multiple whole cell recordings from small networks of cultured hippocampal neurons showed that LTP induction by correlated pre-post stimulation of a pair of connected glutamatergic neurons is accompanied by two forms of spread of potentiation (102): a "retrograde spread" to the inputs onto the dendrite of the presynaptic neuron and a "presynaptic lateral spread" of potentiation to synapses made by the presynaptic neuron onto other postsynaptic cells. The spread of potentiation in this culture system was specific in three aspects: *1)* there was no "forward (anterograde) spread" of potentiation to the output synapses of the postsynaptic neuron. *2*) There was no "postsynaptic lateral" spread of potentiation to converging inputs onto the postsynaptic neuron made by other presynaptic neurons, suggesting that input specificity of LTP is preserved. *3*) Presynaptic lateral spread was found only for glutamatergic terminals that innervate other glutamatergic neurons, but not GABAergic neurons.

How does one reconcile the finding of the restricted LTP spread in cultured hippocampal slices (29) with the absence of LTP spread in dissociated cell cultures described above? One possibility is that the average distance between synapses made by converging inputs in dissociated cell cultures exceed 70 μm, the extent of spread found in slice cultures. Alternatively, the disorganized distribution of synaptic sites in dissociated neurons may have reduced the magnitude and spatial distribution of the spread signal. The target cell-specific presynaptic lateral spread of LTP is reminiscent of the target cell-specific action of brain-derived neurotrophic factor (BDNF) found in these hippocampal cultures, where BDNF-induced potentiation of glutamatergic synaptic transmission was observed only for synapses made onto glutamatergic but not GABAergic neurons (91). It is possible that BDNF signaling associated with LTP induction results in a retrograde signaling, e.g., internalized endosomes containing active BDNF-trkB complexes, that spread to presynaptic nerve terminals onto other unstimulated postsynaptic cells. By having target cell specificity, correlated activity-induced LTP may still preserve some aspect of the input specificity. Given such presynaptic lateral spread of LTP, synaptic modification may be restricted to the set of presynaptic nerve terminals of the same axon that innervate the same type of postsynaptic target cells. Finally, it appears that the spread of potentiation is restricted entirely to the synapses received or made by the presynaptic neuron involved in LTP induction. This is reminiscent of the finding of global enhancement of excitability of the presynaptic neuron following LTP induction in these cultures (see above, Ref. 42), suggesting similar retrograde signaling may be involved in both phenomena.

For GABAergic synapses, lateral spread of synaptic modification was examined in cultured hippocampal neurons (115). No presynaptic spread of modification by correlated pre- and postsynaptic spiking was observed between divergent outputs of the same GABAergic neuron onto two different postsynaptic cells. However, for convergent GABAergic synapses onto the same postsynaptic neuron, substantial spread of modification to unstimulated inputs was observed in some cases. The variability in the extent of the spread may result from differences in the relative dendritic location of the convergent inputs.

Extensive retrograde and lateral spread of LTD has also been observed in cultures of hippocampal neurons, using the conventional protocol of pairing presynaptic stimulation with steady postsynaptic depolarization (32). Whether spike timing-dependent LTD exhibits similar spread remains to be determined. However, in acute hippocampal slices, Nishiyama et al. (81) showed that LTD induced by post-pre spiking at Schaffer collateral-CA1 pyramidal cell synapses spreads extensively to other converging inputs to the same postsynaptic pyramidal cell, although LTP induced at the same synapses by pre-post spiking is input specific. The induction of homo- and heterosynaptic LTD requires functional ryanodine receptors and inositol trisphosphate ($InsP_3$) receptors, respectively. Interestingly, pharmacological blockade or genetic deletion of type 1 $InsP_3$ receptors leads to a conversion of LTD to LTP and the elimination of heterosynaptic LTD, whereas blocking ryanodine receptors eliminates only homosynaptic LTD. These results suggest that postsynaptic Ca^{2+} elevation derived from both Ca^{2+} influx and differential release of Ca^{2+} from internal stores through ryanodine and $InsP_3$ receptors can regulate both the po-

larity and the spread of spike timing-dependent synaptic modification. An $InsP_3$ receptor-dependent Ca^{2+} wave in the postsynaptic neuron may underlie the spread of Ca^{2+} elevation throughout the postsynaptic dendrite, leading to the spread of LTD.

C. Spread of LTP/LTD In Vivo

The findings on the spread of LTP/LTD in cultured cells or slice preparations raise the question of whether similar spreads occur in vivo. Recent studies using intact retinotectal system of developing *Xenopus* tadpoles have addressed this issue. In this system, LTP induced by correlated pre-post spiking of the retinal ganglion cell (RGC) and tectal neuron was found to be input specific throughout early development; there was no spread of potentiation laterally to other converging RGC inputs on the postsynaptic tectal cell or to synapses made by the same RGC axons to other adjacent tectal cells (103). However, LTP of the same retinotectal synapses induced by conventional TBS of RGCs was found to spread extensively to other inputs during the early stages of development, and input specificity of this LTP emerged as the tectal cell develops more elaborate dendritic arbors (103). This difference in the input specificity of LTP induced by correlated spiking and TBS during early development points to an important distinction of STDP. Compared with the conventional forms of LTP, STDP may code for a more specific form of synaptic modification that requires a more precise pattern of spiking activity. Fluorescence Ca^{2+} imaging showed that a global Ca^{2+} elevation in these young tectal neurons was triggered by TBS but not by repetitive correlated spiking (103), suggesting that the input specificity may be attributed to a more localized postsynaptic Ca^{2+} elevation. The emergence of input specificity appears to correlate with the development of spatially restricted domains of Ca^{2+} elevation in the tectal cell dendrite triggered by each retinal axon input, consistent with the idea that Ca^{2+} signaling may participate in the spread of LTP.

The most intriguing observation on the spread of LTP/LTD in hippocampal cultures is the rapid retrograde (or "back-propagation") of potentiation/depression to the synaptic inputs onto the dendrite of the presynaptic neuron. Recent study in the retinotectal system suggests that extensive back-propagation of synaptic modification may also exist in vivo. Persistent potentiation of retinotectal synapses by application of BDNF at the tectum is accompanied by a potentiation of synaptic inputs to the dendrite of the RGCs, leading to increased light-evoked RGC response (25). The BDNF effect at the dendrite depends on TrkB expression in the RGCs and is absent when the optic nerve is severed. Further analysis showed that a rapid increase of AMPA receptors at the RGC dendrites was induced by the exposure of retinotectal synapses to BDNF. This retrograde synaptic modification is similar to the back-propagation of LTP found in cultured hippocampal neurons, suggesting retrograde transport of signals via uptake of factors at the nerve terminal may provide a mechanism for the spread of LTP/LTD in the presynaptic neuron. The same signal may also account for the bidirectional modification of global intrinsic excitability of the presynaptic neuron (see above).

Recent studies have further shown that LTP/LTD of *Xenopus* retinotectal synapses induced by TBS/low-frequency stimulation of the optic nerve is accompanied by a long-range retrograde spread of potentiation/depression from the RGC axon terminals to the synaptic input onto the RGC dendrites. Such retrograde potentiation and depression could be abolished by severing the optic nerve or by blocking the retrograde signaling mediated by BDNF and NO, respectively. Whether spike timing-dependent LTP/LTD also undergo similar retrograde spread remains to be determined. The existence of such long-range retrograde spread of LTP/LTD allows adjustment of the strength of input synapses at the dendrite of a neuron in accordance with that of the output synapses at its axon terminals. Such a mechanism may be useful for a coordinated circuit refinement, in which activity-dependent potentiation/depression of the outputs of a neuron will be used by the circuit to carry out corresponding changes in its input signals, resulting in the consolidation of correct pathways.

VII. CONCLUDING REMARKS

While much progress has been made over the past decade in understanding the role of spike timing in long-term synaptic modification, research in this area is still at its infancy. Most of our current knowledge of STDP is based on studies of excitatory synapses on pyramidal cells. Given the diversity of cell types and their distinct biophysical properties, there is likely to be a variety of cell type specific STDP windows, which remain to be characterized. How synaptic and nonsynaptic forms of STDP operate in concert to shape the functions of neural circuits is only beginning to be explored. Furthermore, sensory processing and many other behavioral tasks involve sequences of events separated by seconds to minutes. How STDP at the time scale of tens of milliseconds relates to these integrative brain functions is largely unknown. Finally, while this review focuses mainly on experimental studies, computational analysis of the consequences of STDP, especially for circuits involving large populations of neurons, will be critical for our understanding of the function of STDP from synapse to perception.

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