

# Spatiotemporal specificity of synaptic plasticity: cellular rules and mechanisms

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**Abstract.** Recent experimental results on spike-timing-dependent plasticity (STDP) and heterosynaptic interaction in various systems have revealed new temporal and spatial properties of activity-dependent synaptic plasticity. These results challenge the conventional understanding of Hebb's rule and raise intriguing questions regarding the fundamental processes of cellular signaling. In this article, I review these new findings that lead to formulation of a new set of cellular rules. Emphasis is on evaluating potential molecular and cellular mechanisms that may underlie the spike-timing window of STDP and different patterns of heterosynaptic modifications. I also highlight several unresolved issues, and suggest future lines of research.

## 1 Introduction

In 1949, Donald Hebb proposed that “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased” (Hebb 1949). This “neurophysiological postulate” has since become a central concept in neuroscience through a series of classic experiments demonstrating “Hebbian-like” synaptic plasticity, including long-term potentiation (LTP) and depression (LTD), in a large variety of systems (for reviews, see Brown et al. 1990; Bear and Malenka 1994; Malenka and Nicoll 1999; Bi and Poo 2001). Over the past few decades, Hebb's idea has been extended into various forms of correlation-based rules of synaptic modification that have been successfully implemented in unsupervised learning networks as well as in computational models for experience-dependent development of neuronal circuits (Stent 1973; Sejnowski 1977, 1999;

Bienenstock et al. 1982; Sejnowski and Tesauro 1989; Brown et al. 1990; Fregnac and Bienenstock 1998).

Central to Hebb's postulate are two essential properties of activity-dependent synaptic modification: temporal specificity and spatial specificity. In the past, temporal specificity has been interpreted as a requirement of coincidence, summarized in the popular mnemonic: “cells that fire together, wire together” (Zigmond et al. 1999). Spatial specificity has been known as “synapse specificity” – only the synapse experiencing coincident activity is modified (Brown et al. 1990; Malenka and Nicoll 1999). In the past few years, two series of spatiotemporal specificity in synaptic modification: (i) correlated pre- and postsynaptic activity induces different types of synaptic modification depending on the precise spike timing (Bell et al. 1997; Magee and Johnston 1997; Markram et al. 1997; Bi and Poo 1998, 1999; Debanne et al. 1998; Zhang et al. 1998; Egger et al. 1999; Feldman 2000; Nishiyama et al. 2000), and (ii) synaptic modifications induced at one synapse in certain cases are accompanied by heterosynaptic changes at specific neighboring sites (Bonhoeffer et al. 1989; Bradler and Barrionuevo 1989; Kossel et al. 1990; Schuman and Madison 1994; Muller et al. 1995; Cash et al. 1996; Staubli and Ji 1996; Engert and Bonhoeffer 1997; Fitzsimonds et al. 1997; McMahon and Kauer 1997; Cowan et al. 1998; Nishiyama et al. 2000; Tao et al. 2000). These discoveries have important implications for the development and function of neural circuits. In particular, they challenge the conventional understanding of the Hebbian synapse and suggest a new set of rules for activity-dependent synaptic modification. At the same time, they raise intriguing questions regarding the fundamental processes of cellular signaling.

## 2 Temporal specificity of synaptic modifications: spike timing-dependent plasticity

The notion of a coincidence requirement for “Hebbian” plasticity has been supported by classic studies of LTP

and LTD that used a “pairing protocol,” i.e., presynaptic stimulation coupled with prolonged postsynaptic depolarization (Kelso et al. 1986; Sastry et al. 1986; Wigström et al. 1986; Goda and Stevens 1996; Malenka and Nicoll 1999). However, “coincidence” here was loosely defined with a temporal resolution of hundreds of milliseconds to tens of seconds, much larger than the timescale for typical neuronal activity characterized by the action potential (spike) that lasts for a couple of milliseconds. In a natural setting, pre- and postsynaptic neurons fire spikes as their functional outputs. How precisely do such spiking activities have to “coincide” in order to induce synaptic modifications? Experiments addressing this critical issue led to the discovery of spike timing-dependent synaptic plasticity (STDP).

### 2.1 STDP and spike-timing window

Pioneer studies have indeed indicated that the induction of LTP or LTD may depend on more precise temporal relationship between pre- and postsynaptic activation (Levy and Steward 1983; Gustafsson and Wigström 1986). In anesthetized rats, associative LTP of local field excitatory postsynaptic potentials (field EPSPs) can be induced at synapses formed by the weak crossed projection from the entorhinal cortex onto the granule cells in the dentate gyrus of the hippocampus, when it is stimulated at high frequency concurrently with a strong converging ipsilateral entorhinal cortex–dentate gyrus projection (Levy and Steward 1979). Interestingly, whereas LTP of the weak input could be induced when it was activated concurrently with or before the activation of the strong input by as much as 20 ms, LTD was induced when the temporal order of the stimulation was reversed (Levy and Steward 1983).

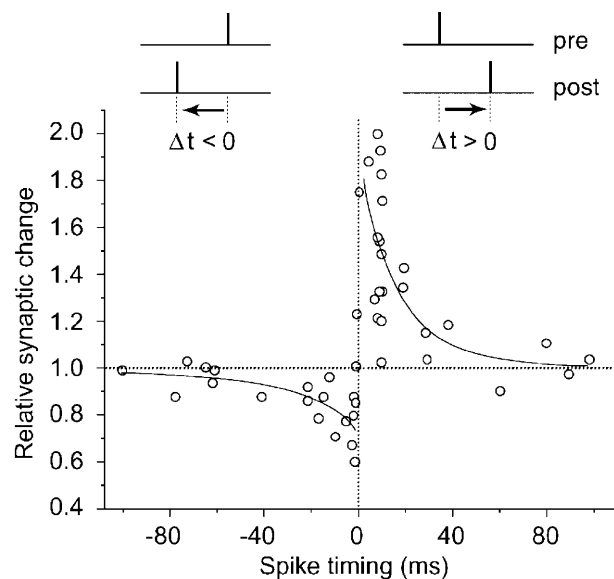
Therefore the requirement for activity-induced synaptic modification is more stringent than the loosely defined “coincidence.” This notion has been further extended into a clear picture of temporal specificity by the demonstration of STDP at the single-cell level. Using simultaneous whole-cell recording from two interconnected layer V pyramidal neurons, Markram et al. (1997) found that repetitive co-stimulation of the two cells – with postsynaptic spikes following presynaptic spikes by 10 ms – induced LTP, whereas stimulation of the two cells at reversed temporal order induced LTD. In hippocampal slices, Magee and Johnston (1997) found that subthreshold synaptic inputs into a CA1 pyramidal neuron, when paired with postsynaptic stimulation, could amplify backpropagating dendritic action potentials (spikes), resulting in synaptic  $\text{Ca}^{2+}$  influx and LTP. These elegant studies unequivocally demonstrated the critical roles of postsynaptic spikes and spike timing in synaptic modification.

STDP has been explored in a variety of systems ranging from cell cultures to in vivo preparations (Bell et al. 1997; Magee and Johnston 1997; Markram et al. 1997; Mehta et al. 1997; Bi and Poo 1998, 1999; Debanne et al. 1998; Zhang et al. 1998; Egger et al. 1999; Feldman 2000; Han et al. 2000; Nishiyama et al. 2000;

Sjöström et al. 2001; Yao and Dan 2001; Froemke and Dan 2002). In many studies, a characteristic asymmetric window of spike timing has been observed (Fig. 1). This provides a quantitative basis for the formulation of a temporally asymmetric Hebbian learning rule (Abbott and Blum 1996; Gerstner et al. 1996; Gerstner and Abbott 1997; Kempter et al. 1999; Roberts 1999; Fusi et al. 2000; Senn et al. 2000, 2002; Song et al. 2000; van Rossum et al. 2000; Kempter et al. 2001; Rao and Sejnowski 2001; Rubin et al. 2001; Song and Abbott 2001). The temporal asymmetry in STDP apparently endows neural circuits with the capability to detect and learn the temporal structure of input stimuli (Berninger and Bi 2002). Such properties may also underlie some forms of navigational map formation (Abbott and Blum 1996) and classical conditioning (Roberts 1999) suggested by network models, as well as experimentally observed asymmetric expansion of receptive fields in the hippocampus (Mehta et al. 1997, 2000) and the visual cortex (Schuett et al. 2001; Yao and Dan 2001). Interestingly, although other types of spike-timing windows have been observed at synapses made by different cell types (Bell et al. 1997; Egger et al. 1999), the asymmetric window (similar to that shown in Fig. 1) is ubiquitous for synapses between pyramidal neurons.

### 2.2 Temporal integration of STDP

An important technical detail worth mentioning is that in most experiments of STDP, repetitive applications of



**Fig. 1.** Spike-timing-dependent synaptic plasticity observed in hippocampal neurons. Each data point represents the relative change in the amplitude of evoked postsynaptic current after repetitive application of *pre-* and *postsynaptic* spiking pairs (1 Hz for 60 s) with fixed spike timing  $\Delta t$ , which is defined as the time interval between pre- and postsynaptic spiking within each pair. Long-term potentiation (LTP, +) and depression (LTD, -) windows are each fitted with an exponential function  $\Delta W^{\pm} = A^{\pm} \exp(-\Delta t/\tau^{\pm})$ .  $A^{\pm} = 0.86, -0.25$ ;  $\tau^{\pm} = 19, -34$  ms. Adapted from Bi and Poo (1998)

pre- and postsynaptic spike pairs were used to induce consistent synaptic modifications. In studies using hippocampal cultures, 60 spike pairs were applied at 1 Hz for each trial of STDP induction (Bi and Poo 1998). Thus for each data point in the spike-timing window (Fig. 1), the amount of STDP  $\Delta W$  (for a specific spike timing  $\Delta t$ ) is the accumulative result of all these spike pairs. For theoretical studies, one would like to know how much synaptic change is introduced by each single activity event, i.e., the effective unitary STDP ( $\delta w$ ) resulting from each single spike pair. How to derive  $\delta w$  from  $\Delta W$  actually depends on the exact rule of such accumulation or integration. For example, as has been assumed in many theoretical studies (Kempster et al. 1999; Song et al. 2000), a simple additive rule can be written as

$$\Delta W = \Sigma \delta w = \delta w \times 60 .$$

Alternatively, the integration may follow a multiplicative rule for the 1-Hz repetitions, thus

$$1 + \Delta W = \Pi(1 + \delta w) = (1 + \delta w)^{60} .$$

The difference between the additive and multiplicative rules is not very prominent for the purpose of deriving  $\delta w$  when  $\delta w$  itself is small, and the number of repetitions of spike pairs is not too large. But in a natural setting, a synapse continuously experiences pre- and postsynaptic spike trains. For the long-term behavior of neural networks, different forms of integration may actually lead to distinct consequences. For example, after random stimulation, a bimodal equilibrium distribution of synaptic weights may result from the linear, additive integration of STDP with a “hard” boundary condition (Song et al. 2000). In contrast, a unimodal distribution is achieved if the integration is multiplicative (van Rossum et al. 2000; Rubin et al. 2001). Furthermore, it has been found that in cortical slices, the induction of STDP depends on the frequency of the repetitive spike pairing – no LTP can be induced when the repetition is below 10 Hz (Markram et al. 1997). This frequency dependence can be accounted for by a sigmoid dependence of LTP induction on membrane depolarization in these neurons (Sjöström et al. 2001). In this case, a single event of paired spiking is insufficient to induce LTP and it is thus questionable whether one can derive any meaningful unitary modification  $\delta w$ .

Even in the case that single spike pairing does induce unitary STDP, and that integration of sparse spike pairs over long periods of time follows simple additive or multiplicative rules, difficulty may still arise when dealing with natural activity patterns. In such cases, multiple spikes (either pre- or postsynaptic) may occur within tens of milliseconds, the same timescale of the STDP spike-timing window. Therefore, how such pre- and postsynaptic spike trains interact with each other becomes a complex issue. Taking a reductionist approach, one may regard the spike-timing window (results of interacting single spike pairs) as a basic set of rules, on top of which multiple spike pairs interact following “secondary” rules of integration. The simplest form of

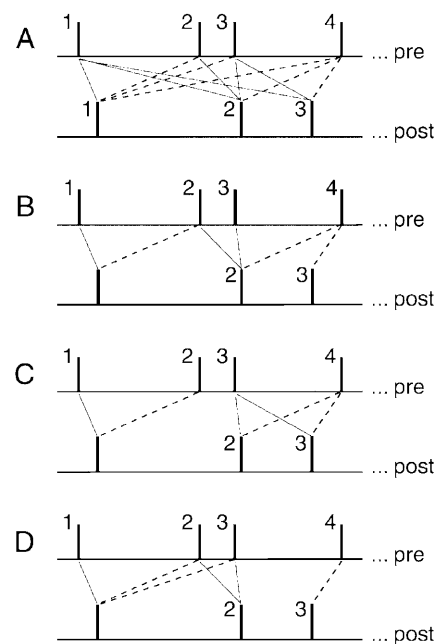
linear integration (Kempster et al. 1999; Song et al. 2000; Fig. 2A), involves two assumptions. First, every presynaptic spike  $i$  pairs with every postsynaptic spike  $j$  to produce STDP ( $\delta w_{ij}$ ) depending on individual spike timing ( $\Delta t_{ij}$ ):

$$\delta w_{ij} = \alpha^{\pm} \exp(-\Delta t_{ij}/\tau^{\pm}) .$$

Here  $\alpha^{\pm}$  and  $\tau^{\pm}$  are unique constants for potentiation (+, if  $t > 0$ ) or depression (–, if  $t < 0$ ), as described in the spike-timing window. Second, the final resultant synaptic change is the linear summation of contributions from all such events:

$$\Delta W = \Sigma \delta w_{ij} .$$

As discussed at the beginning of this section, the integration can also take other forms, such as multiplication. However, a critical question is: does every presynaptic spike interact with every postsynaptic spike, or more generally, do all such interactions contribute equally to produce synaptic modifications? In fact, there is no biological reason a priori that this has to be the case. An alternative to the above simple scheme of spike interaction is a “nearest-neighbor interaction” wherein only the *first presynaptic event* after a given *postsynaptic spike* may produce depression; and only the *first postsynaptic spike* after a given *presynaptic event* may produce potentiation (van Rossum et al. 2000; Fig. 2B). There could also be other forms of near-neighbor interaction. For example, a “postcentric rule” could be that only the first presynaptic event before/after a given postsynaptic spike may produce potentiation/depression



**Fig. 2A–D.** Temporal integration of STDP. Schematics illustrate different ways in which pre- and postsynaptic spike trains may interact to forming spike-pairs (see text). *Solid lines* indicate spike pairs with positive spike timing. *Dotted lines* indicate pairs with negative spike timing. **A** All-to-all interaction. **B** Nearest-neighbor interaction. **C** Postsynaptic-centric interaction. **D** Presynaptic-centric interaction

(Fig. 2C). Similarly, a “precentric” rule could be that only the first postsynaptic spike before/after a given presynaptic event may produce LTD/LTP (Fig. 2D).

The above formulation assumes independence between the effects of different spike pairs. In reality, adjacent LTP- and LTD-inducing pairing events may interact with each other owing to the complexity of intracellular signaling (discussed in Sect. 2.3). Indeed, in hippocampal culture and layer V of rat visual cortex, LTP-inducing pairing appears to exert a dominant effect over LTD-inducing pairing (Bi and Poo 1998; Sjöström et al. 2001). On the other hand, in layer II/III of the visual cortex, it appears that the first spike pair – regardless of it being LTP or LTD inducing – dominates the modification (Froemke and Dan 2002). Therefore, the issue of STDP integration is complicated by nonlinear interactions that may be different at different types of synapses. The functional consequences as well as the cellular mechanisms of such nonlinearity in STDP integration remain to be explored by both theoretical and experimental studies.

### 2.3 Calcium mechanisms underlying STDP

The ultimate description of the rules for STDP and its integration must come from a deep understanding of the underlying cellular and molecular mechanisms. In order to detect the relative timing of pre- and postsynaptic activity, the synapse has to be informed whether and when the postsynaptic cell fires an action potential. Although the action potential is usually initiated at the soma or axon of the postsynaptic neuron, it can backpropagate into dendrites and synapses (Stuart and Sakmann 1994; Buzsáki et al. 1996; Hoffman et al. 1997; Migliore et al. 1999) by virtue of the active properties of dendrites (Lasser-Ross and Ross 1992; Regehr et al. 1992; Johnston et al. 1996). At the synapse, the exact signaling processes leading to synaptic modification are still not well understood. However, it is generally believed that a transient increase in intracellular  $\text{Ca}^{2+}$  is of crucial importance as in most other forms of synaptic plasticity (Artola and Singer 1993; Zucker 1999). In hippocampal slices, pairing of EPSPs with backpropagating dendritic spikes results in synaptic  $\text{Ca}^{2+}$  influx that is correlated with the induction of LTP (Magee and Johnston 1997). In addition, STDP is found to depend critically on functional *N*-methyl-D-aspartate receptors (NMDARs) that are highly permeable to  $\text{Ca}^{2+}$  (Magee and Johnston 1997; Markram et al. 1997; Bi and Poo 1998; Debanne et al. 1998; Zhang et al. 1998; Feldman 2000; Nishiyama et al. 2000). This is consistent with classic studies on LTP and LTD induced by various protocols (for reviews, see Cotman et al. 1988; Madison et al. 1991; Bliss and Collingridge 1993; Linden and Connor 1995).

**2.3.1 Calcium dependence and the paradox of the spike-timing window.** Regarding the roles of intracellular  $\text{Ca}^{2+}$  in long-term synaptic modification, the most popular model can be summarized as follows: high-level intra-

cellular  $\text{Ca}^{2+}$  elevation activates certain protein kinases including the calcium/calmodulin-dependent kinase II (CaMKII) and leads to subsequent LTP, whereas moderate-level  $\text{Ca}^{2+}$  elevation activates phosphatases (e.g., calcineurin) and results in LTD (Lisman 1989; Malenka et al. 1989; Malinow et al. 1989; Artola and Singer 1993; Mulkey et al. 1994). This picture of calcium dependence has been supported by elegant experiments that directly manipulate and monitor postsynaptic  $\text{Ca}^{2+}$  levels (Hansel et al. 1997; Yeckel et al. 1999; Cho et al. 2001; Cormier et al. 2001). At the first look, it also appears to explain nicely the spike-timing dependence of STDP, because when presynaptic stimulation immediately precedes a postsynaptic spike, the backpropagating postsynaptic spike presumably removes the  $\text{Mg}^{2+}$  block at the NMDAR (Mayer et al. 1984; Nowak et al. 1984) thereby causing high-level  $\text{Ca}^{2+}$  influx into the synapse (Magee and Johnston 1997; Koester and Sakmann 1998), whereas when presynaptic stimulation follows the postsynaptic spike, only low-level  $\text{Ca}^{2+}$  influx may occur through voltage-gated calcium channels and the partially blocked NMDARs.

However, if we consider the whole spike-timing window for STDP, the simple scenario of calcium dependence in fact cannot easily explain the asymmetric window shape. Instead, it would predict an additional LTD window in the positive spike-timing range. This can be understood intuitively as follows. Assume that paired spiking with very short but positive spike-timing results in sufficient calcium influx through NMDARs that in turn leads to LTP. Then with increasing  $\Delta t$ , the amount of calcium influx should decrease continuously as glutamate binding to NMDARs decreases. Therefore, before the level of calcium elevation decreases to the nonplasticity-inducing regime, there has to be a range of timing within which the  $\text{Ca}^{2+}$  increase is moderate, i.e., LTD inducing according to the model. However, such an additional LTD window was not observed in most studies that have mapped out the asymmetric spike-timing window of STDP (Bi and Poo 1998; Debanne et al. 1998; Zhang et al. 1998; Feldman 2000; Sjöström et al. 2001; Yao and Dan 2001; Froemke and Dan 2002). The only exception was found in hippocampal slices, where spike timing of 20 ms indeed resulted in LTD (Nishiyama et al. 2000). But this could be due to activation of local inhibitory circuitry by the stimulation, a possibility that may be tested by performing the experiments in the presence of GABA receptor antagonists. The same study also found that blocking the release of  $\text{Ca}^{2+}$  from intracellular stores, while likely reducing the total cytosolic  $\text{Ca}^{2+}$  increase, led to a conversion from LTD to LTP (i.e., negative timing resulted in LTP).

**2.3.2 Dynamic calcium transients and intracellular signaling.** How do we explain the seemingly paradoxical observations from the studies of STDP? One possibility is that during the induction of STDP, local  $\text{Ca}^{2+}$  transients at the synapse are highly dynamic; under such conditions, not only the level but also the spatial and temporal dynamics of  $\text{Ca}^{2+}$  transients could be important in determining the selective activation of

downstream signaling processes and resultant synaptic modification. Indeed, LTP or LTD induced by postsynaptic photolysis of caged  $\text{Ca}^{2+}$  depends critically on not only the level but also the time course of the light-induced  $\text{Ca}^{2+}$  transient (Yang et al. 1999; Zucker 1999). In contrast, when the process of intracellular  $\text{Ca}^{2+}$  elevation is slow, as perhaps in some experiments discussed earlier (Hansel et al. 1997; Cho et al. 2001; Cormier et al. 2001), the condition for subsequent enzymatic reactions may be more close to a steady-state situation; therefore the overall level of  $\text{Ca}^{2+}$  elevation could become the only crucial parameter in determining the resultant LTP/LTD.

Indirect evidence for a dynamic picture of synaptic modification comes from the highly organized complexity of the postsynaptic density and nearby structures (Scannevin and Huganir 2000; Sheng and Sala 2001). In fact, it has been shown that  $\text{Ca}^{2+}$  influxes from different channels appear to activate preferentially different kinase signaling pathways (Deisseroth et al. 1998; Graef et al. 1999; Dolmetsch et al. 2001; West et al. 2001). This could be due to physical proximity of specific kinases with specific channels, or alternatively, distinct contributions of different channels to the temporal dynamics of intracellular  $\text{Ca}^{2+}$  transients. For the second possibility, it is known that even in simple biochemical assays, CaMKII can respond differently to  $\text{Ca}^{2+}$  oscillation at different frequencies (De Koninck and Schulman 1998). It remains to be further examined what spatiotemporal patterns of  $\text{Ca}^{2+}$  transients are triggered during the induction of STDP, and how downstream signaling enzymes are activated.

Additional complexity comes from the intriguing roles of intracellular  $\text{Ca}^{2+}$  stores (Berridge 1998; Svoboda and Mainen 1999; Rose and Konnerth 2001). In all eukaryotic cell types, including neurons, the endoplasmic reticulum extends throughout the cell. The lumen of the endoplasmic reticulum stores  $\text{Ca}^{2+}$  at a high concentration. These  $\text{Ca}^{2+}$  ions can be released via two types of channels: the ryanodine receptors and the inositol 1,4,5-trisphosphate (IP3) receptors (Berridge 1998). Whereas both types of receptors are  $\text{Ca}^{2+}$  sensitive, IP3 receptors are also activated by metabotropic glutamate receptors. Compared to influx through synaptic channels and receptors,  $\text{Ca}^{2+}$  release from intracellular stores is generally slow but long lasting and more global. Although it is still controversial whether and how intracellular  $\text{Ca}^{2+}$  stores are involved in synaptically evoked  $\text{Ca}^{2+}$  signaling (for review, see Svoboda and Mainen 1999), the spatiotemporal pattern of store release may be especially effective for certain signaling enzymes/networks leading to specific synaptic modification. Indeed, it has been shown that in CA1 of the hippocampus, inhibiting store release appeared to block the induction of LTD, and under some conditions even reverse it to LTP (Futatsugi et al. 1999; Nishiyama et al. 2000). In contrast, at mossy fiber-CA3 synapses,  $\text{Ca}^{2+}$  store release mediated by metabotropic glutamate receptors appears to be responsible for LTP induced by high-frequency mossy fiber stimulation with ionotropic glutamate receptor blockade (Yeckel et al. 1999).

Therefore the situation could be further complicated by different experimental conditions and/or by different signaling networks that “readout” the  $\text{Ca}^{2+}$  dynamics.

Taken together, instead of the classical picture that calcium level determines synaptic modification, the following may better describe what occurs during STDP. Rapid (and high-level)  $\text{Ca}^{2+}$  elevation at the postsynaptic density, characteristic of influx through activated NMDARs (with transient removal of  $\text{Mg}^{2+}$  block), is most likely to engage LTP-inducing processes while perhaps inhibiting LTD-inducing processes. Slow and prolonged  $\text{Ca}^{2+}$  increase, typical of store release, tends to engage LTD-inducing processes while perhaps inhibiting LTP-inducing processes. At the “paradoxical zone” of the spike-timing window as discussed in Sect. 2.3.1, the rapid but lower-level  $\text{Ca}^{2+}$  elevation may be too low to engage LTP processes, and too fast to engage LTD processes (or fast enough to actively inhibit LTD processes). In short, the dynamic nature of  $\text{Ca}^{2+}$  transients and enzymatic interactions must be considered in any biophysical model of STDP. Eventually such a mechanistic model may also explain the temporal integration of STDP. Experimentally, quantitative studies using imaging and pharmacological approaches are needed to characterize the spatiotemporal patterns of  $\text{Ca}^{2+}$  transients triggered by different spiking paradigms.

#### *2.4 Diversity and molecular determinants of the spike-timing window*

A variety of spike-timing windows have been observed in different systems (for recent reviews, see Abbott and Nelson 2000; Bi and Poo 2001). In rat somatosensory cortex, STDP has been observed at vertical inputs from layer IV to layer II/III pyramidal neurons (Feldman 2000). The spike-timing window is asymmetric, with positive timing leading to LTP and negative timing leading to LTD, similar to that found in hippocampal cultures (Bi and Poo 1998). But the width of the LTD window is  $>100$  ms, significantly broader than that for hippocampal neurons or that for the lateral connection between layer V pyramidal neurons (Markram et al. 1997). Interestingly, in the same cortical area, synapses between layer IV spiny stellate neurons appear to have a symmetric depression window (Egger et al. 1999). Furthermore, in the cerebellum-like structure of the electric fish, synapses formed by the parallel fibers onto Purkinje-like cells have an asymmetric window but of opposite polarity: pre- and postsynaptic spiking with positive spike-timing induces associative LTD, and repetitive presynaptic stimulation induces nonassociative LTP (Bell et al. 1997; Han et al. 2000).

The diversity of spike-timing windows is not totally surprising. As discussed, many channel molecules contribute to the transient elevation of  $\text{Ca}^{2+}$  triggered by pre- and postsynaptic spiking activity. Downstream of  $\text{Ca}^{2+}$ , many protein kinases and phosphatases form intricate signaling networks. An interesting possibility is that certain key molecules may determine specific quantitative aspects of STDP, for example, the width of

the asymmetric spike-timing windows. In some systems, both L-type  $\text{Ca}^{2+}$  channels and NMDARs are necessary for the induction of LTD by spiking paradigms. If the induction requires overlap between  $\text{Ca}^{2+}$  transients via the two routes, the kinetics of L-type channels may be crucial in determining the width of the LTD window. For the LTP window, evidence suggests two prime candidates: the NMDA receptor and the A-type  $\text{K}^+$  channel. As discussed above, the opening of NMDA receptor depends on both glutamate binding and membrane depolarization that removes its  $\text{Mg}^{2+}$  block (Mayer et al. 1984; Nowak et al. 1984). In other words, this molecule can serve as a molecular detector for the temporal correlation between presynaptic input and postsynaptic spiking. It is thus possible that the kinetics of NMDA receptors quantitatively determines the width of the LTP window. An NMDAR is composed of different subunits, including NR1 and one or more NR2 isoforms (e.g., NR2A, NR2B). Different subunit compositions of NMDAR result in distinct channel kinetics (e.g., NR1/NR2A channels are in general much faster than NR1/NR2B and NR1/NR2A/NR2B channels; Flint et al. 1997; Vicini et al. 1998; Cull-Candy et al. 2001). In cultured hippocampal neurons at the stage of STDP experiments, the time constant of NMDA currents is of the order of 100 ms (J. Dutta, G. Bi, unpublished data, 2002), several times longer than the width of the LTP window. This discrepancy is likely to exist in other systems as well and may be accounted for by nonlinear activation of downstream effectors (e.g., calcium/calmodulin and protein kinases). Alternatively, instead of NMDAR, dendritic A-type  $\text{K}^+$  channels that can be rapidly inactivated by subthreshold EPSPs (Johnston et al. 2000) may determine the window by gating the backpropagation of dendritic spikes (Hoffman et al. 1997; Magee and Johnston 1997; Migliore et al. 1999). These possibilities may be directly tested by molecular manipulations. For example, if the NMDAR hypothesis is correct, then altering the subunit expression in the postsynaptic neuron may change the overall channel kinetics and thereby change the width of the LTP window. Interestingly, the expression of NMDAR subunits naturally changes during development: NR2B is expressed early in development and is later replaced by NR2A expression (Williams et al. 1993; Monyer et al. 1994; Sheng et al. 1994; Kirson et al. 1999). It remains to be investigated how such a developmental switch may affect the spike-timing window of STDP.

Perhaps the most intriguing case is the apparent opposite polarity of the spike-timing window observed in electric fish. The cellular mechanism underlying such STDP in GABAergic Purkinje-like neurons is not yet completely understood, but NMDAR activation and postsynaptic calcium influx are shown to be required for associative depression, but not for potentiation in the same system (Bell et al. 1997; Han et al. 2000). This contrasts dramatically with STDP in synapses between pyramidal neurons. Interestingly, at parallel fiber–Purkinje cell synapses in the mammalian cerebellum, LTP can be induced by low-frequency presynaptic stimulation (for review, see Hansel et al. 2001), a protocol that

is conventionally used to induce LTD of pyramidal neurons in the hippocampus and the neocortex. At the same synapses, LTD is induced by very strong parallel-fiber stimulation alone or weaker parallel-fiber stimulation paired with strong climbing-fiber stimulation, analogous to the conditions for conventional LTP induction in pyramidal neurons. Therefore, synaptic modification in the parallel-fiber synapse in both fish and mammalian systems appear to require opposite activity conditions compared to the pyramidal synapses. Here, it is interesting to note that the functional output of Purkinje cells are inhibitory, also opposite to that of the pyramidal neurons. Mechanistically, the inversion of the synaptic modification rule in such synapses could be due to either different patterns of activity-triggered  $\text{Ca}^{2+}$  dynamics (resulting from both influx through channels and release from stores), or alternatively, a different “readout” of the  $\text{Ca}^{2+}$  dynamics by the downstream kinase/phosphatase signaling networks in the postsynaptic Purkinje or Purkinje-like neurons. Again, it is possible that only a few key molecules actually determine the polarity of STDP. If this is the case, one may be able to alter the polarity by molecular manipulations at different brain areas. This is particularly interesting because of the functional and philosophical implications of “causality detection” of normal STDP and the asymmetric spike-timing window in pyramidal synapses (for detailed discussion, see Berninger and Bi 2002).

### 3 Spatial specificity of synaptic modifications: heterosynaptic interaction

Although not explicitly stated in Hebb’s postulate, it is generally accepted that Hebbian synaptic modifications are synapse specific – only synapses experiencing correlated (or coincident) activity become modified. In other words, synaptic modifications can be regarded as “local” processes, during which individual synapses are independent of one another. Such a concept of spatial specificity has brought beneficial simplicity into neural network models (Brown et al. 1990; Rolls and Treves 1998). On the other hand, it also limits the options of “biologically plausible” learning algorithms in such models. For example, the computationally powerful “backpropagation” algorithm (Rumelhart et al. 1986) is often regarded “nonbiological” because it requires nonlocal spread of error signals from one synaptic site to another (Rolls and Treves 1998). In many experimental systems, synapse specificity was indeed observed by classic studies of LTP and LTD (Andersen et al. 1977; Lynch et al. 1977; Dudek and Bear 1992; Mulkey and Malenka 1992; Nicoll and Malenka 1997). On the other hand, there is growing evidence that induction of synaptic modifications (including both conventional LTP/LTD and STDP) at one set of synapses (hereafter referred to as “homosynaptic” modifications) are often accompanied by changes at some neighboring synapses that did not experience the induction activity (hereafter referred to a “heterosynaptic” modifications) (for review, see Bi and Poo 2001). The cellular mechanisms and

functional consequences of such heterosynaptic interactions remain to be further investigated.

### 3.1 Different forms of heterosynaptic interaction

Studies during the past few decades have demonstrated the complexity of heterosynaptic interactions. In various slice preparation, different types of heterosynaptic modification have been observed. These results may seem a little confusing at first look, but based on the topological relationship between the sites of homosynaptic induction and the sites of heterosynaptic modification they can be categorized into two phenomenological groups: (i) those involving converging inputs onto the same postsynaptic cells (postsynaptic interaction) (Fig. 3A), and (ii) those involving diverging outputs from the same presynaptic cells (presynaptic interaction) (Fig. 3B). More specific patterns of heterosynaptic interaction have been observed in cultured networks.

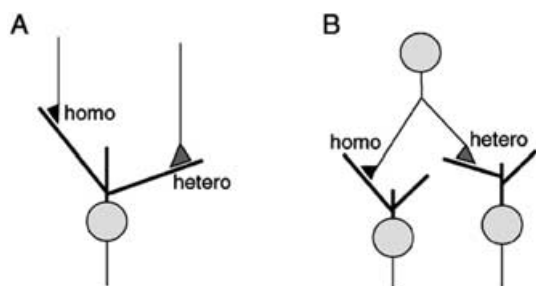
**3.1.1 Postsynaptic interactions.** The most studied case of heterosynaptic interaction is so-called heterosynaptic LTD (for review, see Linden and Connor 1995; Bear and Abraham 1996), a phenomenon first found in hippocampal slices where a depression of unstimulated commissural-CA1 synapses was observed following LTP-inducing tetanic stimulation of Schaffer collaterals (Lynch et al. 1977; Dunwiddie and Lynch 1978). Heterosynaptic LTD was later observed in the cortex (Tsumoto and Suda 1978; Hirsch et al. 1992), dentate gyrus (Levy and Steward 1979; Abraham and Goddard 1983) and the CA3 area (Bradler and Barrionuevo 1989) of the hippocampus, as well as at embryonic neuromuscular junctions in culture (Lo and Poo 1991).

Studies have also shown that in the CA1 area of the hippocampus, homosynaptic LTD induced by low-frequency stimulation at one of two independent inputs was associated with LTD at the other (Muller et al. 1995; Staubli and Ji 1996). Similar heterosynaptic

depression was also found in excitatory synapses onto GABAergic interneurons in the hippocampal CA1 area (McMahon and Kauer 1997; Cowan et al. 1998). These phenomena are sometimes called “postsynaptic spread of LTD” to distinguish them from the conventional heterosynaptic LTD in which it is LTP that is actively induced at the homosynaptic sites. It is likely that both the conventional heterosynaptic LTD and the postsynaptic spread of LTD share common cellular mechanisms, e.g., postsynaptic spread of  $Ca^{2+}$  elevation mediated by some form of regenerative waves (discussed in Sect. 3.3.1). Hereafter, the two types of heterosynaptic phenomena will not be distinguished, and the term “heterosynaptic LTD” will generally refer to both unless otherwise specified.

Also in the hippocampus, heterosynaptic LTP (Miszgeld et al. 1979; Bradler and Barrionuevo 1989) has been observed following tetanic stimulation-induced homosynaptic LTP at other input pathways. A technical limitation in such studies using field stimulation and recording is that the physical locations of the synapses, either formed by the homosynaptic pathway or by the heterosynaptic pathway, are not resolved. Using intracellular recording combined with a local superfusion technique, Engert and Bonhoeffer (1997) found that in hippocampal slice cultures, LTP induced at one defined location by “pairing” presynaptic stimulation with prolonged postsynaptic depolarization could spread to another site (up to 70  $\mu\text{m}$  away from the induction site) on the same postsynaptic neuron. In this particular case, the homosynaptic and heterosynaptic sites are indeed on the same postsynaptic neuron. However, in one of their experimental configurations, presynaptic stimulation was applied to the same axonal fibers, which may bifurcate to form multiple synaptic contacts within a certain range on the same postsynaptic neuron; therefore the observed heterosynaptic LTP could also be consistent with the definition of presynaptic interaction.

**3.1.2 Presynaptic interactions.** Studies of presynaptic interactions were made possible by intracellular and whole-cell patch-clamp recordings. In slice cultures, Bonhoeffer et al. (1989) found that LTP induced by pairing presynaptic stimulation with postsynaptic depolarization is accompanied by potentiation at synapses made by the stimulated fiber on neighboring postsynaptic cells. A similar “spread” of potentiation was also observed in the visual cortex, where the spread of potentiation was shown to occur only for synapses made by the stimulated, but not unstimulated, inputs (Kossel et al. 1990). In acute hippocampal slices, pairing-induced LTP in CA1 pyramidal cells also spread to synapses made by the same set of afferent fibers onto neighboring postsynaptic cells (Schuman and Madison 1994). Presynaptic spread of LTD was first clearly demonstrated in a culture system where a *Xenopus* motor neuron innervates two different myocytes. Following the induction of LTD at one neuromuscular synapse by photolysis of caged  $Ca^{2+}$  in a postsynaptic myocyte, Cash et al. (1996) found that such LTD can spread to the synaptic

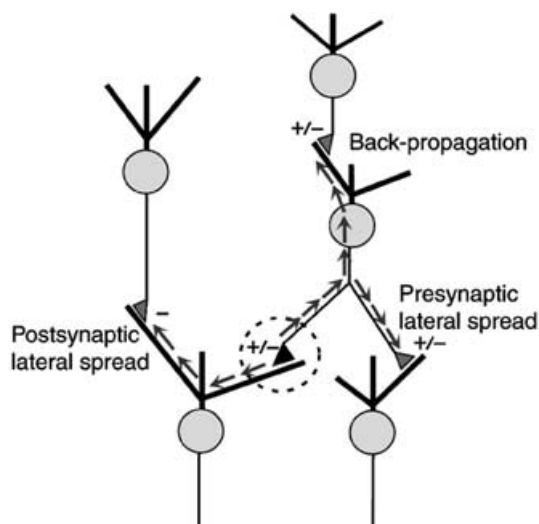


**Fig. 3A,B.** Basic forms of heterosynaptic interaction – induction of synaptic modification at one site (*homo*, black triangle) affect the efficacy of another (*hetero*, gray triangle) – based on observations made in slice preparations. **A** Postsynaptic interaction. For homosynaptic LTP, both heterosynaptic LTP and LTD have been observed; for homosynaptic LTD, only heterosynaptic LTD has been observed. **B** Presynaptic interaction. For both homosynaptic LTP and LTD, only heterosynaptic modifications of the same sign (spread of LTP/LTD) have been observed

connection from the same presynaptic neuron on the other myocyte that is hundreds of microns away.

**3.1.3 Specific patterns of heterosynaptic interaction in cultured neuronal networks.** As discussed in Sects. 3.1.1 and 3.1.2, various forms of heterosynaptic interactions are observed in different experimental studies. An immediate question is: do all or some of these phenomena coexist in the same system? This question is difficult to address in many preparations because detailed analysis of the pattern of heterosynaptic interactions is technically challenging due to the complexity of native circuitry. The use of simultaneous whole-cell patch-clamp recording in cultured small neuronal networks partially overcomes this difficulty. In such a simplified system (consisting of three or four neurons), the activity of each neuron in the circuit can be under external control and the synaptic currents of all possible connections can be monitored. Because LTP or LTD induction involves both pre- and postsynaptic neurons, the induction can be specific to a particular synaptic connection in the network, whereas possible changes recorded at other synapses should reflect a rather comprehensive picture of heterosynaptic interaction.

In cultured networks of hippocampal neurons, specific patterns of heterosynaptic modification were observed following the induction of LTP or LTD at a particular synaptic connection (Fitzsimonds et al. 1997; Tao et al. 2000; Fig. 4). It appears that LTP and LTD both can spread to synapses made by other outputs of the same *presynaptic* neuron (“presynaptic lateral propagation”). However, only LTD (i.e., not LTP) spreads to those synapses made by other inputs on the same *postsynaptic* cell (“postsynaptic lateral propagation”). Intriguingly, both LTP and LTD can apparently spread in the retrograde direction to synapses made by other neurons onto the dendrites of the presynaptic



**Fig. 4.** Pattern of heterosynaptic interaction based on results in cultured neuronal networks. For both homosynaptic LTP (*plus* symbols) and LTD (*minus* symbols), only heterosynaptic modifications of the same sign have been observed. See text for details

neuron (“backpropagation”). On the other hand, neither LTP nor LTD can spread in the anterograde direction to the output synapses of the postsynaptic neuron (“forward propagation”). Finally, neither LTP nor LTD was found to spread further up- or downstream beyond the immediate neighboring synapses (“secondary propagations”).

In summary, certain types of heterosynaptic interaction (e.g., presynaptic spread of LTP) has been observed in different preparations. On the other hand, not all types of heterosynaptic interaction observed in one preparation were found in others. This is in part due to technical difficulties. For example, backpropagation has not been examined at all in conventional slice preparations. It is also possible that the exact forms of heterosynaptic interaction indeed differ in different systems, and/or different developmental stages (as discussed in Sect. 3.3.1). Nevertheless, these studies suggest that nonlocal synaptic interaction, though maybe in different forms, is a rather ubiquitous cellular phenomenon. Therefore, one cannot always regard synaptic modifications as isolated, local events, but must also consider the direct or indirect interaction among different (neighboring) synapses. For experimentalists, this phenomenon suggests intriguing cell biological processes that must be explored.

### 3.2 Signaling properties of heterosynaptic interactions

A crucial question regarding the cellular basis of heterosynaptic modifications is: what molecular factors carry the signals for synaptic modification from one synapse (the induction site) to the other (the heterosynaptic site)? Obviously, the final answer to this question requires a better understanding of the directly induced homosynaptic modifications. Conversely, investigating heterosynaptic modifications will also provide insights into the nature and signaling mechanisms of homosynaptic modifications themselves.

In general terms, one may describe the process of activity-induced synaptic modification as a series of signaling events, probably starting with correlated activity and postsynaptic  $\text{Ca}^{2+}$  influx, and ending with presynaptic and/or postsynaptic changes, e.g., insertion of AMPA receptors (Malinow et al. 2000). If a signaling factor generated at a particular step is nonlocal, i.e., able to spread beyond the synapse where it is produced, by either diffusing extracellularly or spreading within the cytoplasm (of either the presynaptic or the postsynaptic cell), it could eventually act on neighboring sites and result in heterosynaptic modifications. Presumably, common downstream signaling components exist at both the homosynaptic and the heterosynaptic sites; therefore, heterosynaptic modifications could have the same expression mechanisms as those of homosynaptic LTP and LTD.

Heterosynaptic signaling through extracellularly diffusible factors has been suggested by elegant experimental studies. In hippocampal slices, pairing-induced LTP at one set of synapses formed by the input fibers

onto a pyramidal neuron could spread to another set of synapses between the same input fibers onto a neighboring neuron, as long as the two neurons are no further apart than 50  $\mu\text{m}$  (Schuman and Madison 1994). Interestingly, it was also found that the spread (as well as the homosynaptic induction) of LTP was blocked by inhibiting the production of the gaseous second messenger nitric oxide (NO) in the postsynaptic cell. Because NO diffuses readily across the cell plasma membrane, it may also serve as an extracellularly diffusible factor for heterosynaptic signaling.

However, the effective concentration of a synaptically generated, extracellularly diffusible factor such as NO decreases rapidly with increasing spreading distance  $r$  (proportional to  $1/r^3$ , e.g., decreases to  $\sim 1/1000$  for  $r = 10 \mu\text{m}$ , assuming a 1- $\mu\text{m}$  synapse size) even before considering its short lifetime as a free radical. Thus the range of such extracellular spreading is very limited. This may not be a serious problem for the 50- $\mu\text{m}$  distance between the two postsynaptic neurons because the actual distance between synaptic sites could be much shorter due to the extensive overlap between the dendritic branches of the two cells (Schuman and Madison 1994). However, as discussed in Sect. 3.1.1, spreading of LTP in slice cultures could occur from one locally superfused site to another that is as far as 70  $\mu\text{m}$  away (Engert and Bonhoeffer 1999). In addition, the fluid control of local superfusion itself also limits any free diffusion out of the targeted spot by rapid removal of superfusion solution. Thus an extracellularly diffusible factor (NO) alone is unlikely to mediate the observed spread, instead, these results may be explained by a two-step mechanism: the postsynaptic neuron first produces a short-range (diffusible) factor which in turn activates a long-range intracellular signal that propagates within the presynaptic input fibers. Two superfused sites that are close to each other, or two postsynaptic cells with overlapping dendrites, tend to receive more inputs from axonal branches of the common fibers; therefore a presynaptic intracellular signal could mediate the spread of LTP between the two sites. On the other hand, sites that are too far apart could only receive inputs from different fibers and thus be unable to exhibit any spread.

A clear and direct demonstration of long-range intracellular signaling in heterosynaptic interaction came from studies in cultured *Xenopus* neuromuscular synapses (Cash et al. 1996). In this system, LTD induced by transient elevation of postsynaptic  $\text{Ca}^{2+}$  in one myocyte could spread over hundreds of microns to another synapse made by the same motor neuron on another myocyte. This heterosynaptic depression could not have been mediated by an extracellularly diffusible factor because clearance of extracellular fluid could not prevent the spread, and because no depression was induced by increasing  $\text{Ca}^{2+}$  in a nearby myocyte not innervated by the same presynaptic neuron. In cultured networks of hippocampal neurons, the extent and specificity of propagations (Fig. 4) also suggest that such heterosynaptic interactions are mediated by intracellular factors, but the possibility of mediation by extracellularly diffusible factors could not be ruled out (Fitzsimonds et al. 1997;

Tao et al. 2000). One reason is that conventional multiple patch-clamp methods used in the studies can only record the ensemble response from many synaptic boutons that distribute rather haphazardly along the dendrites of a neuron, whereas the dendrites from different neurons often intermingle within a network, making it difficult to determine the actual relationship between the inducted and propagated synaptic sites. This problem can be solved if one can directly study synaptic responses and plasticity at physically identified boutons. Using a local puffing method, we have recently been able to induce STDP at such identified boutons (P. Lau, G. Bi, unpublished data, 2002). It remains to be examined whether and how such modifications may spread, in what directions, to what extents, and at what speeds. In addition, future studies should also determine, in neuronal networks, how the induction and propagation signals generated at multiple synapses integrate to result in final outcomes of synaptic modifications. Such information is needed for formulating quantitative rules of heterosynaptic interaction.

### 3.3 Potential mechanisms for long-range intracellular signaling

If long-range intracellular signaling mediates heterosynaptic interaction, the patterns of propagation of LTP and LTD revealed by culture studies must reflect distinct signaling routes, i.e., postsynaptic lateral propagation being mediated by dendritic signals and presynaptic lateral propagation being mediated by axonal signals. Backpropagation must involve both axonal and dendritic signals. In addition, there are possibly two signs (LTP and LTD) for each type of signaling. The nature of such signals is still unknown. Here I discuss several potential mechanisms that are consistent with existing experimental evidence. These examples are not intended to give a full explanation for different types of heterosynaptic interaction, but rather to illustrate some general principles in such long-range intracellular signaling.

#### 3.3.1 Postsynaptic (dendritic) signaling – $\text{Ca}^{2+}$ mechanisms.

As discussed in Sect. 2.3, transient elevation of intracellular  $\text{Ca}^{2+}$  at the postsynaptic cell is the most crucial step in the signaling process for activity-induced synaptic plasticity. If such  $\text{Ca}^{2+}$  transients spread beyond the range of a single postsynaptic site, they could directly cause heterosynaptic modifications. However, despite its small size, the mobility of the  $\text{Ca}^{2+}$  ion in the cytoplasm is very low due to intracellular buffering and homeostatic regulation (Neher 1998). In mature neurons, the spread of synaptic  $\text{Ca}^{2+}$  is further restricted by the geometry of dendritic spines (Müller and Connor 1991; Yuste and Denk 1995; Nimchinsky et al. 2002). Therefore passive diffusion of  $\text{Ca}^{2+}$  ions is in general not sufficient to mediate postsynaptic spread of synaptic modifications. In tectal neurons of early developing *Xenopus* tadpoles, significant spread of dendritic  $\text{Ca}^{2+}$  has been observed following theta burst stimulation of retinal ganglion cells (Tao et al. 2001).

This  $\text{Ca}^{2+}$  spread indeed correlated with the observed postsynaptic spread of theta burst-induced LTP, as both types of spread disappeared in more developed animals. The spread of  $\text{Ca}^{2+}$  here could be due to passive diffusion that overcomes the buffering and regulating mechanism in the immature dendrites, or alternatively it could also be due to an active mechanism that involves release from intracellular  $\text{Ca}^{2+}$  stores.

It is known that both the ryanodine receptors and the IP<sub>3</sub> receptors are sensitive to intracellular  $\text{Ca}^{2+}$  (Berridge 1998). Therefore they may support a process of calcium-induced calcium release, leading to regenerative  $\text{Ca}^{2+}$  waves (Berridge 1998; Nakamura et al. 1999; Kapur et al. 2001). Such an active propagation often travels rapidly over long distances along dendrites, thus it can serve as a good candidate for mediating some forms of long-range heterosynaptic modification. Indirect evidence for a role of  $\text{Ca}^{2+}$  waves in heterosynaptic modifications comes from studies in area CA1 of the hippocampus, where functional blockade of IP<sub>3</sub> receptors led to a conversion of homosynaptic LTD to LTP and elimination of the postsynaptic spread of LTD (Nishiyama et al. 2000). Intriguingly, blocking ryanodine receptors eliminated only homosynaptic LTD, leaving LTD at the heterosynaptic site intact (Nishiyama et al. 2000). It appears that in this system, IP<sub>3</sub> receptors play a major role in mediating the waves of  $\text{Ca}^{2+}$  store release, which in turn are responsible for LTD at the heterosynaptic site. Direct imaging studies are needed to further evaluate the contribution of different types of store release to the spatiotemporal pattern of  $\text{Ca}^{2+}$  transients during the induction of homo- and heterosynaptic modifications.

**3.3.2 Retrograde and presynaptic (axonal) signaling.** Besides postsynaptic long-range signaling in heterosynaptic modification, several lines of evidence also indicate the existence of presynaptic signaling. Because of the crucial role of the postsynaptic cell (and its  $\text{Ca}^{2+}$  transients) in synaptic modifications, the first step of presynaptic signaling must begin with a retrograde messenger that is generated or activated at the postsynaptic site and acts on its presynaptic counterpart (for a recent review on retrograde signaling, see Tao and Poo 2001). A well-known example is the gaseous messenger NO that is synthesized by a postsynaptic enzyme NO synthase in response to intracellular  $\text{Ca}^{2+}$  elevation (Hawkins et al. 1998). As discussed in Sect. 3.2, such an extracellularly diffusible factor could mediate interaction between immediately adjacent synapses. But more generally, a retrograde messenger may locally activate downstream events at the presynaptic sites and generate intracellular signaling factors that propagate within the presynaptic cell over longer distances. Similarly, retrograde messenger may also be generated/activated downstream of the postsynaptic spread signal and in turn initiate possible presynaptic expression of modifications.

Although the identity of the signaling factor(s) for long-range presynaptic spread remain elusive, results from other studies have provided useful clues. For example, it is known that NO can activate cytoplasmic

guanylyl cyclase that synthesizes intracellular messenger cyclic GMP (cGMP), which in turn activates cGMP-dependent kinases, and may lead to LTP of presynaptic transmitter release (Hawkins et al. 1998). Because cGMP can diffuse rather freely within the cytoplasm, it may actually mediate some forms of presynaptic spread of LTP. Besides cGMP, another cyclic nucleotide cAMP is also involved in different forms of synaptic plasticity (Bailey et al. 1996; Blitzer et al. 1998; Wong et al. 1999). Imaging studies have shown that cAMP can diffuse rapidly in neuronal cytoplasm (Hempel et al. 1996). In developing *Xenopus* motor neurons, locally stimulating adenylyl cyclase that produces cAMP has been shown to exert long-range actions on distant parts of the neuron (Zheng et al. 1994). In *Aplysia*, restricted application of serotonin (5-HT) to the cell bodies of sensory neurons can cause long-term enhancement at synaptic connections of the same sensory neuron to distant motor neurons (Clark and Kandel 1993; Emptage and Carew 1993). Taken together, cyclic nucleotides have the potential to serve as intracellular messengers for mediating long-range heterosynaptic interaction.

Besides the gaseous retrograde messengers such as NO that diffuse across cell membrane and act directly on intracellular enzymes, other molecules such as neurotrophins (Marty et al. 1997) and endocannabinoids (Wilson et al. 2001) may be secreted by the postsynaptic cell upon postsynaptic  $\text{Ca}^{2+}$  increase, and may modulate presynaptic transmitter release by activating presynaptic receptor kinases (Tao and Poo 2001). It is possible that the downstream effectors of these kinases spread passively or actively within the presynaptic cell and act at heterosynaptic sites to induce synaptic modifications. Another possibility is that neurotrophin-binding receptors may be endocytosed into the presynaptic cell and then travel to other sites by protein motor-based transport along cytoskeleton tracks (Vale et al. 1985; Vallee and Bloom 1991; Kuznetsov et al. 1992; Bi et al. 1997). The speed of such active transport can be up to a few microns per second, slower than some fast  $\text{Ca}^{2+}$  waves or diffusion of small molecules over short distances, but may still be sufficient for most forms of presynaptic spreading. A similar transport could carry synaptic signals to the nucleus, where gene transcription is modulated for longer-term changes. Furthermore, the vesicles may go across the somata to the dendritic ends of the “presynaptic” cell, where the internalized ligand molecules may be released again to activate receptors on other neurons that innervate the “presynaptic” cell, thus resulting in backpropagation of synaptic modification. Future experiments that examine the specific temporal requirements of different spreading could evaluate the feasibility of these mechanisms. In addition, carefully designed molecular and pharmacological manipulations could provide more direct tests.

#### 4 Cellular rules for the growth of a cell assembly?

Hebb's postulate of correlated activity-dependent synaptic modification was proposed to provide a

mechanism for the formation of a cell assembly, a small circuit of interconnected neurons that may function as the basic unit of perception (Hebb 1949). In Hebb's theory, the cell assembly is capable of responding to specific external input with a sequence of firing activity, which may reverberate within the circuits for a fraction of a second. Such reverberating activity then constitutes a transient "memory trace." At the same time, the activity may induce slower but long-lasting synaptic modifications (according to Hebb's rule) that reinforce specific connections to facilitate future reactivation of the previously "learned" activity patterns. The formation of a stable assembly thus represents the conversion from short-term into long-term memory. How would such processes, or the functional development of neuronal circuits in general, be influenced by the newly discovered spatiotemporal properties of synaptic modifications?

The temporal asymmetry in the spike-timing window (Fig. 1) fits well into Hebb's considerations. The causality requirement in the firing order of pre- and postsynaptic neuron to a large extent ensures that the sequential firing in the circuit and subsequent synaptic modification is a positive-feedback process, thus likely to promote the growth of the right assembly. Exactly how such an assembly may develop and how stably it may function must be further evaluated by both theoretical and experimental studies. On the other hand, the functional consequences of heterosynaptic spreading of synaptic modifications are less obvious. In fact, spreading of LTP/LTD reduces the independence of different synapses, thus apparently reducing the memory capacity of a network. However, a nonlocal error or reward signal may improve the learning power of a network as demonstrated by the backpropagation algorithm. In addition, under certain conditions (e.g., early in development) or in the early phase of assembly growth, a less restricted pattern of modification may be beneficial for rapid establishment of a "coarse" circuit that can be later refined by more specific modifications. It is of interest to find out whether and how such heterosynaptic interaction may differ under different developmental and neuromodulatory conditions. Interestingly, a spatial asymmetry exists in the spread of spiking-induced LTP in hippocampal cultures: only the synapses associated with the presynaptic neuron (with regard to the induction site) experience heterosynaptic potentiation. Thus presynaptic lateral propagation of LTP would increase the overall influence of a successful presynaptic neuron, and backpropagation would further strengthen its sensitivity to upstream inputs. Again, whether and how such effects may be involved in the formation of stable cell assemblies remain to be examined.

The past decades have seen accelerated progress in our understanding of the physiology of neurons. Now, in the spirit of Hebb, and with modern molecular, cellular, physiological, and computational tools, we are in the position to understand synaptic plasticity in terms of quantitative spatiotemporal rules. These fundamental rules are likely to bridge the gap between synaptic

physiology and neural network behavior, and serve as building blocks for our ultimate understanding of the development and function of the nervous system.

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