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Temporal asymmetry in spike timing-dependent synaptic plasticity

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Abstract

Activity-dependent synaptic modification is critical for the development and function of the nervous system. Recent experimental discoveries suggest that both the extent and the direction of modification may depend on the precise timing of pre- and postsynaptic action potentials (spikes). This phenomenon, termed spike timing-dependent plasticity (STDP), provides a new, quantitative interpretation of Hebb's rule and raises intriguing questions regarding the fundamental processes of cellular signaling. In this article, we summarize previous results obtained in a hippocampal culture system, where an asymmetric window of spike timing was found for paired pre- and postsynaptic spiking to induce STDP. We also discuss our recent studies using a "triplet-spiking" paradigm that reveals nonlinear, temporally asymmetric integration of STDP.

Keywords: Hebb; Synaptic plasticity; Spike timing; STDP; Temporal integration; Hippocampal culture

1. Introduction

In the vertebrate brain, myriads of interconnected neurons form intricate circuits. To perform cognitive functions such as learning and memory, a neuronal circuit needs to reconfigure its connectivity according to the activity patterns it experiences. The reconfiguration involves activity-dependent synaptic modifications, including both strengthening (or potentiation) and weakening (or depression), which are also believed to underlie the experience dependent shaping of highly ordered brain circuits during development. The essential question is: What is the logic that underlies the decision for a synapse to be strengthened or weakened, or in other words, what are the "rules" of activity-dependent synaptic modification?

The most famous rule of synaptic modification was proposed by Donald Hebb [1]: "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." This "neurophysiological postulate" has since become a central concept in neuroscience as a series of classic experiments demonstrated "Hebbian-like" synaptic plasticity, including long-term potentiation (LTP) and depression (LTD), in a large variety of systems (for reviews, see Refs. [2–5]). Central to Hebb's postulate is a strict temporal specificity, which in the past has been interpreted as a coincidence requirement, summarized in the popular mnemonic: "cells that fire together, wire together." However, pioneering studies have indicated that not only the loosely defined coincidence, but also the *temporal order* of presynaptic and postsynaptic activation might be crucial in determining synaptic modifications [6,7]. Furthermore, a series of recent experiments in both in vitro and in vivo preparations have firmly established that correlated pre- and postsynaptic spiking activity induces LTP or LTD, depending on precise spike timing, a phenomenon now termed spike timing-dependent synaptic plasticity (STDP).

2. STDP and temporally asymmetric spike-timing window

STDP was first clearly demonstrated in cortical and hippocampal slices [8,9]. In particular, Markram et al. [8] found that repetitive co-stimulation of two interconnected layer V pyramidal neurons, with postsynaptic spike following presynaptic spike by 10 ms, induced LTP, whereas

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stimulation with reversed temporal order resulted in LTD. Similar phenomena were also observed in hippocampal cultures [10,11]. For most synapses between two glutamatergic neurons in such cultures (Fig. 1), LTP was reliably induced by repetitive spiking stimulation of both pre- and postsynaptic neurons (60 pairs, 1 Hz), with the postsynaptic spike following the presynaptic spike within 10 ms (Fig. 2A). In contrast, 60 paired spiking at the same frequency but with the postsynaptic spike preceding the presynaptic spike induced LTD (Fig. 2B). Interestingly, both LTP and LTD induced by the paired spiking requires functional *N*-methyl-D-aspartate receptors (NMDARs) as they are completely blocked by specific NMDAR antagonist D-AP5. This is consistent with studies of LTP and LTD induced by conventional protocols in CA1 of the hippocampus and other brain areas [4,5], suggesting common cellular mechanisms.

Previous studies have systematically examined the precise temporal requirement for paired spiking-induced synaptic modifications by evaluating the effects of various spike timing Δt—the time interval between the presynaptic stimulation and postsynaptic spiking [10]. For this study,

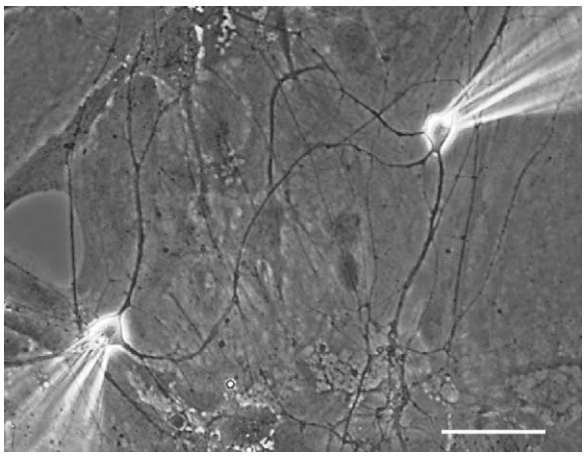

Fig. 1. Dual patch-clamp recording of cultured hippocampal neurons. Low-density cultures of dissociated embryonic (E18) rat hippocampal neurons were prepared as previously described [10,11]. In this preparation, neurons were co-cultured with glial cells on a glass coverslip coated with poly-L-lysine. Pairs of interconnected neurons could be found growing on small patches of glial cells, isolated from the rest of the neurons in the culture. For electrophysiological studies, the external bath solution contained the following (in mM): NaCl 150, KCl 3, $CaCl_2$ 3, $MgCl_2$ 2, HEPES 10 and glucose 5 (pH 7.3). The intrapipette solution contained the following (in mM): potassium gluconate 136.5, KCl 17.5, NaCl 9, $MgCl_2$ 1, HEPES 10, EGTA 0.2 and 200 μg/ml amphotericin B (pH 7.3). Throughout the experiment trial, the culture was continuously perfused with fresh bath medium at a rate of ~1 ml/min. Recordings were carried out with patch-clamp amplifiers (Axopatch 200B or Multiclamp 700A; Axon Instruments, CA. PC505B, Warner Instrument, CT) at room temperature. Signals (filtered at 5 kHz) were acquired at a sampling rate of 10 kHz using a 16-bit digitizing board (DigiData1320, Axon Instruments, or E6035, National Instruments) interfaced with pClamp8 software (Axon Instruments) or a LabView-based customized program. In some experiments, series resistances (15–35 MΩ) were compensated at 80% (lag, 100 μs). In all experiments, there was no change in series resistance or input impedance (200–500 MΩ) following repetitive pairing protocols. Scale: 50 μm.

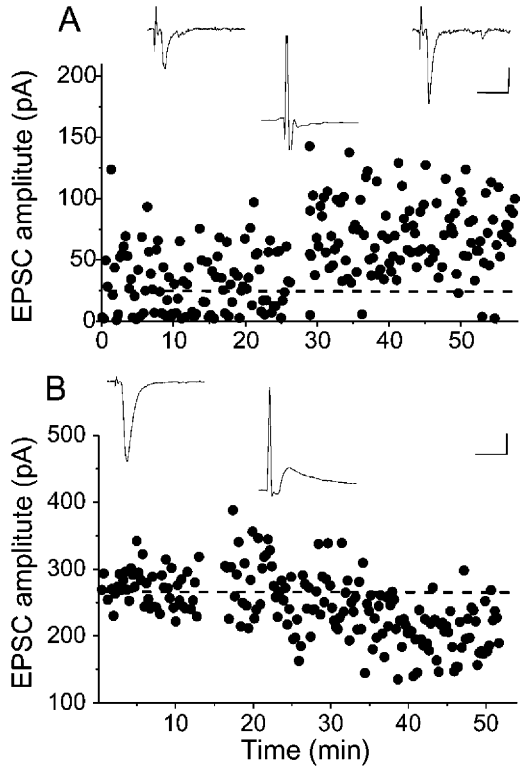

Fig. 2. Induction of LTP and LTD by paired spiking. (A) An experimental trial in a pair of glutamatergic neurons, where LTP was induced by paired spiking (arrow) with spike timing of 5 ms. Insets show an average of five consecutive EPSCs 5 min before (left) and 20 min after (right) the spiking paradigm. Middle inset is an example trace of the EPSP and the spike recorded at the postsynaptic neuron during paired spiking. Scale: 20 pA, 10 ms for EPSCs; 20 mV, 10 ms for EPSP. (B) Another experiment trial in which spike timing was −6 ms. Scale: 100 pA, 10 ms for EPSCs, 30 mV, 10 ms for EPSP. (Adapted from Ref. [10]).

only subthreshold connections between glutamatergic neurons with initial evoked postsynaptic current (EPSC) amplitude less than 500 pA were used because it was found that modification depends also on the postsynaptic cell type and the initial synaptic strength [10]. As shown in Fig. 3, the induced synaptic changes showed a strong but highly asymmetric dependence on spike timing. Potentiation was consistently induced when the postsynaptic spikes peaked within a time window of ~20 ms *after* the presynaptic stimulation, while depression was induced when the spikes peaked within a window of ~30 ms *before* the presynaptic stimulation. The ability for paired spiking to induce potentiation or depression decreases rapidly as the spike timing increases so that outside the 50-ms window, synaptic modification was essentially absent. Importantly, the temporal order of presynaptic stimulation and postsynaptic spiking is of crucial importance, and the transition from maximal depression to maximal potentiation takes less than 5 ms around $\Delta t = 0$.

Similar spike-timing windows for STDP have been observed in several other systems including *Xenopus* retinotectal preparations [12], slice cultures [13], and acute

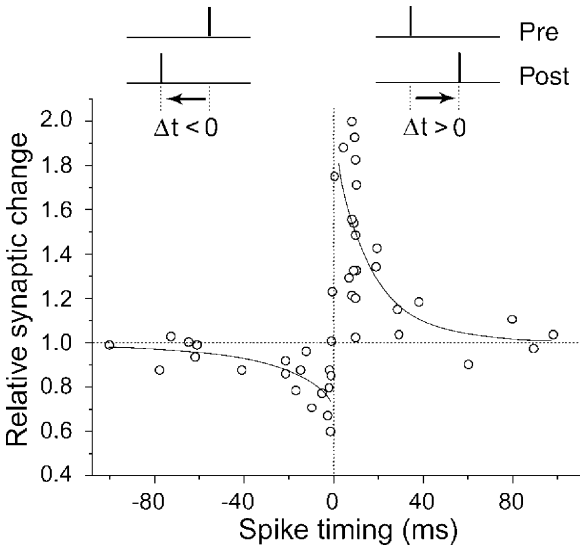

Fig. 3. Spike-timing window of STDP characterized in hippocampal cultures. Each data point represents the relative change in the amplitude of EPSC after repetitive application of pre- and postsynaptic spiking pairs (1 Hz for 60 s) with a fixed spike timing Δt. LTP (+) and LTD (−) windows are each fitted with an exponential function $\Delta W^{\pm} = A^{\pm} \times \exp(-\Delta t/\tau^{\pm})$. $A^{\pm} = 0.86, -0.25$; $\tau^{\pm} = 19, -34$ ms. (Adapted from Ref. [10]).

cortical and hippocampal slices [14–17]. In these studies, the characteristic temporal asymmetry appears to be ubiquitous: in general, LTP is induced when the postsynaptic spike follows the presynaptic spike (positive timing), whereas LTD is induced when the postsynaptic spike fires first (negative timing). The width of the window for effective modification varies in different systems, but is mostly on the order of tens of milliseconds. It is interesting to note that for the induction of STDP (Fig. 1A), the postsynaptic cell must fire action potentials, the functional outputs of neurons in physiological conditions. This "paired spiking paradigm" differs from the conventional "pairing protocol" that consists of presynaptic stimulation coupled with prolonged postsynaptic depolarization (for reviews, see Refs. [4,5]). Ironically, although the conventional pairing protocol has been used in many classic studies to demonstrate "Hebbian plasticity," the spiking paradigm for STDP is even closer to Hebb's original idea: the synapse from cell A to cell B is strengthened only if A "takes parts in *firing*" B.

3. Asymmetric integration of STDP revealed by triplet stimuli

The repetitive paired spiking paradigm has been useful in revealing some essential temporal properties of STDP, i.e. the interaction of single pre- and postsynaptic pairs that occur within tens of milliseconds. However, in a natural setting, a synapse continuously experiences pre- and postsynaptic spike trains that often contain multiple spikes in such a time scale. The final outcome of synaptic modification may then be viewed as integration of several spike pairs, each of which interacts to produce synaptic modification according to the spike-timing window described above. Several theoretical studies have assumed a simple scheme of linear integration in which every presynaptic spike pairs with every postsynaptic spike and the effect of all these pairs adds up to reach the final result of synaptic modification [18,19]. However, there is no biological reason a priori that the integration is linear. In fact, considering the intricate intracellular signaling processes during the induction of STDP, it is likely that the integration is somehow nonlinear. Apparently, the rules for integration must be determined by experiments.

The simplest form of STDP integration involves three interacting spikes ("triplets"): two presynaptic spikes with one postsynaptic spike, or one presynaptic spike with two postsynaptic spikes (Fig. 4A). Of particular interest are triplet types a1 and b1, each of which involves both positive and negative spike timing (and may potentially engage both LTP and LTD mechanisms). Previously, we have explored such integration in a special case: when postsynaptic spiking

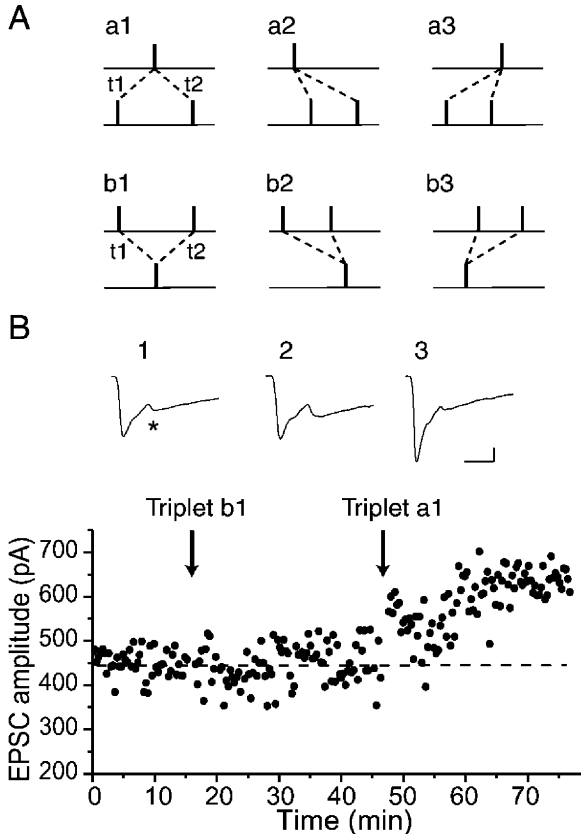

Fig. 4. (A) Triplet configurations for temporal integration of STDP. t1, t2, are spike timings (as defined in Fig. 2) for each spike pair. (B) Asymmetric temporal integration of STDP revealed by a "triplet" experiment. Two different triplet stimuli (middle insets) were applied to the recorded neuron pair at 16 and 47 min (arrows). Each of the three traces (1, 2 and 3) is an average of five consecutive recording at ~10, 40 and 70 min, respectively. Scale: 10 ms, 100 pA. '*' marks a GABAergic polysynaptic component.

is followed by presynaptic activation of a suprathreshold connection, the postsynaptic cell fires a second spike by the input EPSP alone; thus for each presynaptic input, there are two postsynaptic spikes, the first with negative spike timing, the second with positive timing. In this special case of a1 type "triplet," the LTP process (or the second pairing event) appears to dominate [10]. In those cases, however, the spike timing interval for the second pairing t2 was not controlled and was usually shorter than the first interval t1, and thus might have given the LTP-inducing processes a competitive advantage. Therefore, in a recent study, we examined the effects of triplets a1 and b1 on subthreshold synaptic inputs for which postsynaptic spikes were generated by controlled external stimulation. To simplify the situation, we chose $t1 = t2 = 10$ ms for both triplet types. Fig. 4B shows an experiment in which both triplets were examined for the same synapse. Interestingly, whereas little synaptic change was induced following the first triplet stimulation (b1 type), significant LTP was induced following the second triplet (a1 type).

Similar results have been consistently observed in more experiments using the triplet paradigms. The average of seven cases of a1 type experiments shows significant LTP ($31.5 \pm 4.2\%$, mean ± S.E.M.). In contrast, the average of six cases of b1 triplet experiments shows no significant change ($1.2 \pm 2\%$). Therefore, for triplet stimulation, the "rule" of STDP integration is nonlinear and temporally asymmetric: the LTP-inducing pairing appears to dominate when it follows the LTD-inducing pairing; whereas the two opposite pairing events appear to cancel each other when the LTP-inducing pairing occurs first.

4. Diversity and molecular mechanisms of STDP

Besides the typical asymmetric spike-timing window found in synapses between pyramidal neurons, studies in different systems have revealed the diversity of the STDP windows (for recent reviews, see Refs. [5,20]). In the rat somatosensory cortex, vertical inputs from layer IV to layer II/III pyramidal neurons exhibit STDP with an asymmetric spike-timing window [14]. But the width of the LTD window is >100 ms, significantly broader than that for hippocampal neurons [10] or that for the lateral connection between layer V pyramidal neurons [8]. Interestingly, in the same cortical area, synapses between layer IV spiny stellate neurons appear to have a symmetric depression window [21]. Furthermore, in the cerebellum-like structure of the electric fish, synapses formed by the parallel fiber onto Purkinje-like cells have an asymmetric window but of opposite polarity: pre- and postsynaptic spiking with positive spike timing induces associative LTD [22].

Various spike-timing windows must reflect the properties of underlying molecular mechanisms. At the synapse, many molecules including NMDAR, voltage-gated calcium channels, as well as channels on intracellular Ca^{2+} stores may contribute to the transient elevation of Ca^{2+} triggered by pre- and postsynaptic spiking activity. Downstream of Ca^{2+}, many enzymes including protein kinases and phosphatases form intricate signaling networks. An unanswered question is: would certain key molecules determine specific quantitative aspects of STDP? For example, the width of the LTP and LTD windows as shown in Fig. 2 may be determined primarily by the kinetics of NMDAR and voltage-gated calcium channels, respectively. Alternatively, dendritic A-type K^+ channels that can be rapidly inactivated by subthreshold EPSPs [23] may determine the LTP window by gating the back-propagation of dendritic spikes [24]. As for the intriguing case in electric fish, the apparent opposite polarity of spike-timing window could be due to either different Ca^{2+} dynamics being triggered by the same spiking activity, or the same Ca^{2+} dynamics being read out differently by the downstream kinase/phosphatase signaling networks, in the postsynaptic Purkinje-like neurons.

Recent studies using slice preparations have also revealed nonlinearity in STDP integration, but with different integration rules. In layer V of the rat visual cortex, Sjostrom et al. [16] suggested that LTP-inducing pairing might dominate the integration. In contrast, Froemke and Dan [25] suggested that in layer II/III of the visual cortex, integration of STDP followed a "first pairing–dominating" rule: a spike or pairing event that occurs earlier suppresses the effects of later ones. Our results of asymmetric integration are partially consistent with the "LTP-dominating" rule (when the LTP event occurs later) but not with the "first pairing–dominating" rule. It is again possible that different cellular mechanisms operates in various types of pyramidal neurons, thus resulting in different rules of integration.

5. Functional implications

The computational consequences of STDP have been explored by many theoretical studies (for reviews, see Refs. [5,20]). In particular, the temporal asymmetry in the spike-timing window apparently endows neural circuits with the capability to detect and learn the temporal structure of input stimuli, and may serve as the cellular basis for our concept of causality [26]. Such properties may also underlie some forms of navigational map [27] and classical conditioning [28] suggested by network models, as well as experimentally observed asymmetric expansion of receptive fields in the hippocampus [29,30] and in the visual cortex [17,31]. It remains to be explored what effects the different types of integration may have on the development and function of different neuronal circuits.

Finally, it is worthwhile to note that Hebb's postulate was originally proposed to provide a mechanism for the formation of the cell assembly, a small circuit of interconnected neurons that may function as a basic unit of perception [1]. As a quantitative extension of Hebb's concept, the asymmetric window for STDP is likely to be consistent with what

is required for promoting the growth of cell assemblies. Exactly how such an assembly may develop and how stable it may function must be further evaluated by both theoretical and experimental studies. Nevertheless, the discovery of STDP represents an important step in our understanding of synaptic plasticity in terms of quantitative spatio-temporal 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.

Acknowledgements

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