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Ca^{2+} and synaptic plasticity

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Abstract

The induction and maintenance of synaptic plasticity is well established to be a Ca^{2+}-dependent process. The use of fluorescent imaging to monitor changes $[Ca^{2+}]_i$ in neurones has revealed a diverse array of signaling patterns across the different compartments of the cell. The Ca^{2+} signals within these compartments are generated by voltage or ligand-gated Ca^{2+} influx, and release from intracellular stores. The changes in $[Ca^{2+}]_i$ are directly linked to the activity of the neurone, thus a neurone's input and output is translated into a dynamic Ca^{2+} code. Despite considerable progress in measuring this code much still remains to be determined in order to understand how the code is interpreted by the Ca^{2+} sensors that underlie the induction of compartment-specific plastic changes.
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1. Introduction

The activity-dependent modulation of synaptic strength in the hippocampus is the probable neural substrate for the encoding and storage of episodic memory. *Long-term* changes in the efficacy of glutamatergic transmission involve either the *potentiation* (LTP) or *depression* (LTD) of excitatory post-synaptic potentials evoked in response to afferent stimuli. In this chapter, we review the role of Ca^{2+} in the induction and expression of LTP and LTD. We will concentrate on the hippocampus where synaptic plasticity has been most intensively studied, but will also take note of plasticity in other cortical areas such as the cerebellum and sensory neocortex. LTP and LTD can be dissociated into multiple subtypes all in part dependent on the post-synaptic Ca^{2+} dynamics following neural activity. The injection of Ca^{2+} chelators into CA1 pyramidal neurones blocks induction of LTP [1] while conversely the photoactivation of caged Ca^{2+} in these cells induces potentiation [2]. LTD induction shows a similar sensitivity to calcium chelators [3] and photorelease [4]. Generally speaking, it appears that fast, high amplitude elevations in intracellular calcium concentration (Ca^{2+}) lead to potentiation, while smaller and more prolonged signals lead to depression [5].

The development of fluorescent Ca^{2+} indicator molecules and high-resolution laser-scanning microscopy has led to a wealth of data on the kinetics of Ca^{2+} transients in intraneuronal compartments. Despite some limitations with regard to their binding kinetics and mobility, these dyes allow us to deconstruct the spatial and temporal dynamics of Ca^{2+} signals encoding a repertoire of biophysical events. These can then be related to the conditions for induction of synaptic plasticity where, however, our understanding of the many interacting Ca^{2+} sources, secondary messengers and effectors is far from complete. Hippocampal pyramidal neurones receive approximately 10,000 synaptic inputs [6,7], at morphologically discrete sites called dendritic spines. The computational power of these cells depends in part on the capacity to modify the weight of each input independently, in the synapse-specific manner predicted by Hebb [8]. Ca^{2+} enters spines principally by ligand-gated channels and these signals are compartmentalized where they affect local Ca^{2+} sensors. These signals can be amplified and propagated by intracellular Ca^{2+} stores

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along dendrites where different effector targets exist. The activity of ligand-gated channels and intracellular stores is synergistically modulated by the action of voltage-gated Na^+ and Ca^{2+} channels resulting in a system that is exquisitely sensitive to frequency and coincidence of pre-synaptic and post-synaptic activity.

2. Multiple forms of LTP and LTD

2.1. Induction protocols

LTP in CA1 pyramidal neurones is commonly induced by tetanic stimulation of Schaffer collateral afferents (see Fig. 1 for examples of typical LTP- and LTD-inducing protocols). An important advance was the demonstration that the NMDA receptor (NMDAR) antagonist D-2-amino-5-phosphonovalerate (APV) can prevent tetanus-induced LTP, while having little effect on the EPSP evoked by low-frequency test stimuli [9]. Tetanic stimulation causes strong depolarization of the post-synaptic cell, relieving the voltage-linked Mg^{2+} block of the NMDAR channel, and allowing Ca^{2+} to pass into the post-synaptic locus. As will be discussed, this localized Ca^{2+} influx is thought to be the principal trigger for synapse specific LTP. LTP can also be induced by repetitive low-frequency pairing of single afferent stimuli combined with strong depolarizing pulses delivered to the post-synaptic cell [10]. In a related paradigm, called spike-timing dependent plasticity (STDP), the depolarizing pulse is shortened, inducing only a single post-synaptic action potential (AP). As will be discussed, the timing of the pre-synaptic AP relative to a post-synaptic AP back-propagating into dendrites critically determines the kinds of Ca^{2+} signals that are generated and the resultant modulations of synaptic efficacy; LTP is induced if the pre-synaptic spike precedes the post-synaptic spike less than 50 ms, with the degree of LTP diminishing as the interval between pre- and post-synaptic spikes increases (reviewed in [11]).

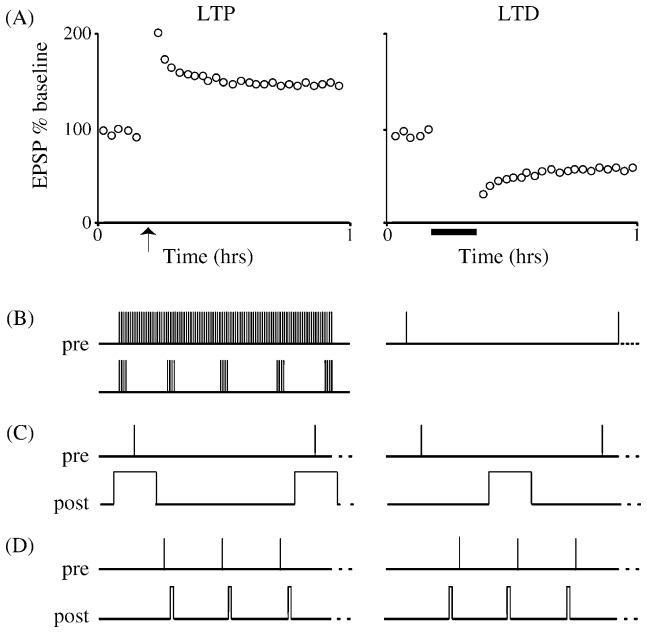

Fig. 1. Schematic representation of plasticity-inducing protocols. (A) A representation of normalized EPSP amplitudes recorded before and after delivery of a high-frequency train (tetanus) marked by the arrow (LTP), or prolonged low-frequency train marked by a bar (LTD). (B) Protocols involving tetanic stimulation of afferent fibres. The illustration at the top left shows a typical tetanus, consisting of 100 pre-synaptic stimuli delivered over 1 s. Beneath this is shown a theta burst protocol consisting of five, short high frequency bursts (e.g. 4 pulses presented at 100 Hz) delivered 200 ms apart at the theta frequency of 5 Hz'. On the right is shown a typical protocol for the induction of LTD, a low frequency train at 1 Hz for 10–15 min. (C) The pairing protocol for LTP induction involves 0.1–1.0 Hz pre-synaptic stimulation at 0.1–1.0 Hz paired with post-synaptic depolarizing pulses to 0 mV for 100 ms, during which the cell fires several APs. Pairing is repeated 50–100 times. When delivered out of phase, as shown on right, the protocol produces LTD. (D) Spike timing-dependent induction protocols involve delivery of pre-synaptic stimuli to produce an EPSP in the impaled cell, timed to precede by10 ms a single backpropagating AP induced in the post-synaptic cell by a narrow depolarizing pulse. When the pre-synaptic stimulus precedes the post-synaptic injection, several repeated pairings will induce LTP, while reversal of the pairing order (right) results in LTD.

LTD can similarly be induced by a range of stimulus protocols, and is also senitive to APV [3,12,13]. Prolonged low-frequency stimulation (typically 1 Hz for 15 min) is effective in young animals, and can also work in older animals if pairs of pulses are delivered at low frequency [14]. LTD is induced by pairing protocols in which the pre-synaptic spike is out of phase with the post-synaptic depolarizing pulse [15] or, in STDP protocols, when the post-synaptic spike precedes the pre-synaptic spike by 50 ms or less [11]. An NMDA receptor-independent form of LTD can also be induced by transient activation of group 1mGluR receptors (reviewed in [16]).

2.2. Early LTP

In the presence of protein synthesis inhibitors, LTP decays to base line within 3–5 h [17]. Thus, we can dissociate this *early* LTP into from a more persistent, protein synthesis-dependent form referred to as *late* LTP. The induction and maintenance of LTP are also have a differential dependence on kinase activity. Inhibition of the enzyme Ca^{2+}/calmodulin-dependent kinase II (CaMKII) prevents the induction of LTP, but maintenance of previously established LTP is unaffected [18–21]. CaMKII depends on Ca^{2+} influx via the NMDAR for its activation, as influent calcium ions are rapidly bound by the mobile buffer calmodulin. Calmodulin is a fundamental second messenger that triggers adenylate cyclase production of cAMP as well as CaMKII activation (reviewed in [22]). Early-LTP is thus expressed through the activation of protein kinases that phosphorylate proteins local to the site of Ca^{2+} influx. One such target following synaptic activation is thought to be the AMPA-type glutamate receptor (AMPAR), as shown by application of Ca^{2+}/calmodulin to purified post-synaptic fractions and subsequent phosphorylation of the AMPA R subunit GluR1 [23,24].

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