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Ca^{2+}- and CaMKII-mediated processes in early LTP

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ABSTRACT

Learning methods determine the degree of stimulation of engrams encoding information to be memorised. More enriching modes of learning allow more enduring long-term potentiation of the synapses associated with these memories. The additional activity causes a prolonged increase in [Ca2+] in the dendritic spine of the postsynaptic neuron. This allows Ca^{2+}-mediated molecular pathways to bring about cytoskeletal remodeling, posttranslational modifications, and protein trafficking. These processes contribute to early long-term potentiation of the synapses, strengthening the memory they store and lead to improved performance on tests of memory recall.

KEYWORDS: Long-term potentiation, Calcium/calmodulin-dependent protein kinase II, Signal transduction, AMPARs, Calcium signalling

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Introduction

Learning is the recording of regularities in the environment by selectively strengthening neural connections in the brain. Synapses can be strengthened by long-term potentiation (LTP) caused by specific patterns of stimulation. LTP is divided into an early phase, which occurs independently of protein synthesis, and a late phase, which is protein synthesis-dependent.[1]

When the students memorise a series of symbols, those groups that use a more enriching learning method receive additional stimulation of the synapses comprising the engrams that encode the symbols. This reinforcement allows a long-lived increase in the postsynaptic [Ca^{2+}], promoting the Ca^{2+}- mediated synaptic modifications of early LTP. This permits more effective potentiation of the synapses, and more enduring memories.

When glutamate is released from the synaptic bouton of the presynaptic neuron onto the dendritic spine of the postsynaptic neuron, it binds receptors in the postsynaptic density (PSD). The PSD contains ionotropic glutamate receptors and signalling proteins, and is linked to the actin filaments that comprise the structural framework of the spine.[2] The *N*-methyl-D-aspartate receptors (NMDARs) located in the PSD allow Ca^{2+} to enter the spine upon binding glutamate and a co-agonist. This co-agonist can be glycine; or alternatively, D-serine may bind, playing a role in astroglial regulation of neural plasticity.[3,4] The resulting influx of Ca^{2+} may, with the required pattern of stimulation, lead to LTP.

Ca^{2+}entry into the spine activates Ca^{2+}/calmodulin-dependent protein kinase 2 (CaMKII). CaMKII is the most abundant signalling molecule in the PSD, and is a major messenger and effector in early LTP.[5] At rest, this serine/threonine kinase is bound by filamentous actin (F-actin) and is held away from the PSD. The entry of Ca^{2+} activates calmodulin, which activates CaMKII and causes it to dissociate from actin and translocate into the PSD.[6] Activated CaMKII then becomes autophos-

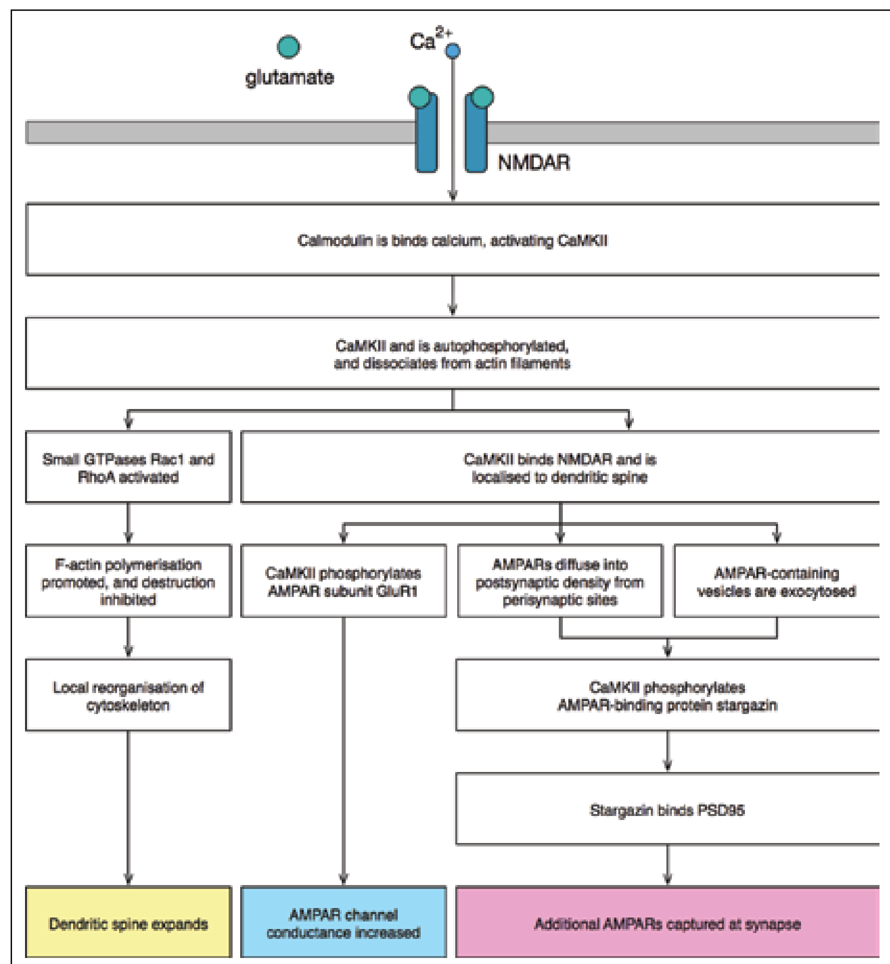

Fig. 1: Simplified outline of CaMKII-mediated processes in early LTP.

phorylated, prolonging its activity beyond when [Ca^{2+}] returns to resting levels.[7] Also, phosphorylated subunits are swapped between CaMKII molecules, which can then phosphorylate other inactive subunits. This spreads the state of phosphorylation, prolonging CaMKII activity.[8]

A network of F-actin forms the framework of the dendritic spine, and CaMKII activation allows remodeling of this cytoskeleton. At rest, F-actin is held in bundles by CaMKII, stabilizing the spine structure. When synaptic activity induces CaMKII, it detaches from F-actin, allowing the cytoskeleton to reorganise.[9] The freed CaMKII phosphorylates the guanine nucleotide exchange factor kalirin-7, which activates the small GTPase Rac1.[10] Rac1 activation ultimately leads to the functional inactivation of cofilin, an actin-binding protein that severs F-actin filaments.[11] A different GTPase, RhoA, is concomitantly activated by CaMKII. RhoA associates with profilin II, which then adds actin monomers to growing filaments.[5] CaMKII eventually returns to its inactive state and binds the reorganised F-actin, re-stabilising the structure. In this way, CaMKII modifies the equilibrium between the construction and destruction of F-actin to allow expansion of the dendritic spine.[12]

Once activated, CaMKII brings about post translational modifications that increase the excitatory post synaptic current (EPSC). α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid receptors (AMPARs) are ionotropic glutamatergic receptors that impart rapid synaptic transmission.[13] CaMKII phosphorylates the AMPAR subunit GluA1 at multiple sitesto increase the conductance of these receptors' ion channels.[14] Phosphorylation increases the efficiency of the coupling between the binding of glutamate and the opening of the ion channel, increasing the amplitude of the EPSC. This is an important step in early LTP.[15]

Increased immobilisation of AMPARs at the PSD synergises with the increase in channel conductance in early LTP. CaMKII inhibits the diffusion of AMPARs at the PSD by phosphorylating the regulatory protein stargazin.[16] The C-terminus of stargazin binds to scaffolding proteins of the PSD to fix the AMPAR at the synapse, restricting diffusion of AMPARs away from the PSD. This functionally intensifies the EPSC.[17]

While AMPAR phosphorylation and immobilisation are mediated by CaMKII, which can remain in its active, autophosphorylated state for a prolonged period, the insertion of additional AMPARs at the PSD depends directly on spine [Ca^{2+}]. AMPARs are recycled at synapses by endocytosis and exocytosis of receptor-containing vesicles.[18] Usually found in the base of the spine, these vesicles need to be transported to the spine head and exocytosed. This increases the number of AMPARs in the PSD, increasing the amplitude of the EPSC as part of early LTP. [19] The class V myosin MyoVb mediates this transport, changing conformation with increased spine [Ca^{2+}]. MyoVb is now able to bind Rab11 family-interacting protein 2, an adaptor protein on receptor vesicles.[20] It then acts as a molecular motor, facilitating vesicle transit along actin filaments from the spine base to the head, where exocytosis can occur. This process is so critical that MyoVb inhibition completely blocks LTP.[21] This Ca^{2+}-triggered trafficking pathway serves the dual purpose of providing additional plasma membrane as the spine grows during LTP (as shown in Figure 1).[19]

Without repeated stimulation, the increase in spine [Ca^{2+}] is probably not prolonged enough to achieve a significant increase in postsynaptic AMPARs. Dendritic spines have a poor intrinsic buffering capacity for Ca^{2+}, and action potentials increase [Ca^{2+}] only very briefly. High-frequency stimulation is required to bring [Ca^{2+}] to a plateau for a longer period.[22] A prolonged increase in [Ca^{2+}] is also achieved by activation of growth factor receptors, which stimulates the release of intracellular Ca^{2+} stores. [23] The activity of autophosphorylated CaMKII is required for LTP: elevated [Ca^{2+}] must be sustained to allow a majority of CaMKII molecules in the spine to become autophosphorylated.[24] This takes up to 2 seconds, with almost all CaMKII molecules being autophosphorylated after 5 seconds.[25]

The dependence of processes in LTP on the duration of increased [Ca^{2+}] in the spine is consistent with students who use a more enriching learning method forming longer-lasting memories. Additional rehearsal of information to be learned can lead to a prolonged surge in spine [Ca^{2+}], allowing these Ca^{2+}-mediated processes of LTP to occur more extensively.

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