

Precise mechanisms of a calcium-dependent kinase during the formation of new memories

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Synaptic plasticity is the ability to strengthen or weaken the synapses or sites of communication between neurons. These changes are triggered by the activation of several different molecules inside small neuronal protrusions called dendritic spines. Although there are different forms of spine plasticity, these distinct forms are all induced by a common signal: the increase of calcium in the dendritic spines. The protein CaMKII is the most abundant protein kinase in the brain and is particularly enriched at synapses where it plays a crucial role in the regulation of synaptic transmission, neurotransmitter release, and synaptic plasticity. Normally, CaMKII is inactive because its binding site is blocked, but calcium removes the blockage, thus activating the protein. Communication through synapses causes calcium concentrations to spike, which activates CaMKII. But it is still a mystery exactly how calcium spike patterns translate into CaMKII activity.

In their May 2017 publication in *Neuron*, MPFI researchers from Ryohei Yasuda's lab described how they optimized existing imaging methods to more precisely visualize CaMKII activation induced by [calcium](#) level increases. By improving the temporal resolution of fluorescence lifetime imaging to the millisecond range, they were able to see for the first time how CaMKII acts during synaptic plasticity in [dendritic spines](#) when calcium spikes occur in quick succession in a single dendritic [spine](#). The researchers used laser pulses to activate single synapses and evoke calcium spikes in dendritic spines in mouse brain slices and then watched what happened to CaMKII activity. The Yasuda team found that CaMKII activity spiked in response to each pulse, just like calcium. But the CaMKII spikes lasted longer than the calcium spikes and combined together in a step-wise fashion. Because the signals combined over time, specific patterns of calcium spikes could

translate into variable amounts of CaMKII activity and thus different changes in synapse strength and structure.

The protein CaMKII can also work independently of calcium if it phosphorylates itself at the site Thr286. This is because autophosphorylation prevents CaMKII's binding site from becoming blocked again. Although this is an important feature of CaMKII's function, it is still unknown how phosphorylation influences CaMKII's translation of calcium signals. To address this question, the Yasuda Lab repeated their experiments with a mutant form of CaMKII that couldn't be phosphorylated at this site. The mutant CaMKII activity spikes were shorter than normal, and as a result, the activity induced by repeated synapse activation did not add up over time. Long-lasting changes in synapse strength and structure were also impaired. However, stimulating the synapse faster, so that the CaMKII spikes could add together, restored the functional and structural changes. These results indicate that Thr286 autophosphorylation is required for the induction of spine plasticity by facilitating calcium integration mediated by CaMKII, but phosphorylation is dispensable for the maintenance of the plasticity.

Future directions

This is the first report that demonstrates the precise filtering mechanisms of a calcium-dependent kinase during the induction of synaptic plasticity in single dendritic spines. The observations of this study clarify the critical role of Thr286 phosphorylation in plasticity: it lowers the stimulation frequency required to induce [synaptic plasticity](#) and permits CaMKII to integrate calcium signals at physiologically relevant frequencies. This provides direct evidence against the long-standing speculation that phosphorylation at Thr286 is the

biochemical correlate for long-term memory.

Future research in the Yasuda Lab is expected to lead to significant advances in the understanding of the molecular signals that regulate memory formation. Because CaMKII function seems to be disturbed in mental diseases, a detailed analysis of this molecule using the advanced imaging methods developed in the Yasuda Lab may provide important insights into the pathogenesis of brain disorders, such as Alzheimer's disease.

More information: Jui-Yun Chang et al, CaMKII Autophosphorylation Is Necessary for Optimal Integration of Ca²⁺ Signals during LTP Induction, but Not Maintenance, *Neuron* (2017). [DOI: 10.1016/j.neuron.2017.04.041](https://doi.org/10.1016/j.neuron.2017.04.041)

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