SYNAPTIC PLASTICITY

Yin and yang

Ca^{2+} /calmodulin-dependent kinase II (CaMKII) is a key regulator of synaptic strength, but the exact mechanisms underlying this regulation are not known. Now, Lisman and colleagues show that the phosphorylation state of the amino acids T305 and T306 of CaMKII determines whether long-term potentiation (LTP) or long-term depression (LTD) is induced.

To investigate the effects of different phosphorylation states of CaMKII on synaptic strength, the authors transfected single cells of cultured hippocampal slices

with various CaMKII constructs. Expression of the active and pseudophosphorylated CaMKII^{T286D} decreased the amplitude of spontaneous AMPAR (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor)-mediated excitatory postsynaptic currents (EPSCs). This result was unexpected as previous studies had implicated CaMKII^{T286D} in the regulation of LTP. The decrease of AMPAR EPSCs in CaMKII^{T286D}-expressing neurons was not observed when slices were incubated with agents that inhibit LTD — the NMDAR (N-methyl-D-aspartate receptor) blocker D(-)-2-amino-5-phosphonovaleric acid (APV, also known as AP5) and the calcineurin inhibitor FK-506, also known as tacrolimus. This suggests that LTD-like processes underlie the depression that was observed in CaMKII^{T286D}-expressing neurons.

The authors suggested that CaMKII^{T286D} might autophosphorylate T305/T306 and that this would prevent enzyme activation by Ca^{2+} /calmodulin. Indeed, expression of the triple mutant CaMKII^{T286D:T305A:T306A}, which cannot be phosphorylated at T305/T306, prevented the development of synaptic depression and led to synaptic potentiation, whereas expression of the triple mutant CaMKII^{T286D:T305D:T306D},

which mimics phosphorylation at all three amino acids, caused synaptic depression. These results suggest that CaMKII^{T286D} causes synaptic depression when T305/T306 is phosphorylated.

Next, the authors tested the effects of different constructs on LTP or LTD in cultured slices. LTD could not be induced in neurons expressing CaMKII^{T286D}, whereas induction of LTP was normal. The neurons expressing CaMKII^{T286D:T305A:T306A} showed the opposite pattern. These results are consistent with the idea that the depression or potentiation resulting from the expression of the mutant CaMKII forms alone occluded further LTD or LTP, respectively. As expected, induction of LTD was blocked in neurons that expressed CaMKII^{T286D:T305D:T306D}. LTP induction was also inhibited in these neurons owing to the inability of the CaMKII mutant to bind Ca^{2+} /calmodulin.

In summary, these results implicate the phosphorylation state of CaMKII at T286 and T305/T306 in the regulation of LTP and LTD.

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ORIGINAL RESEARCH PAPER Pi, H. J. et al. Autonomous CaMKII can promote either long-term potentiation or long-term depression, depending on the state of T305/T306 phosphorylation. *J. Neurosci.* **30**, 8704–8709 (2010)

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