NEUROCHEMISTRY

Ultrasensitive switch

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is crucial for synaptic plasticity at hippocampal synapses, but some facts about its function remain unclear. For example, although CaMKII activity and strong Ca^{2+} elevations are key for the establishment of long-term potentiation (LTP), moderate Ca^{2+} levels are also required for the induction of long-term depression (LTD). What keeps CaMKII from interfering with the induction of LTD? How might Ca^{2+} signals be selectively targeted to CaMKII or to other Ca^{2+}-sensitive enzymes at the synapse? Bradshaw *et al.* took a close look at the biochemical properties of the purified enzyme and found that CaMKII is extraordinarily sensitive to the concentration of Ca^{2+}, providing a possible answer for these questions.

A key feature of CaMKII that allows it to act as a presumptive 'memory molecule' is its ability to phosphorylate itself. Autophosphorylation enables CaMKII to maintain its kinase activity long after the initial increase in Ca^{2+} disappears, forming the core of what has been referred to as a 'bistable switch'. The authors studied the autophosphorylation properties of purified CaMKII as a function of Ca^{2+} and protein phosphatase 1 (PP1), the enzyme in charge of dephosphorylating CaMKII. They found a steep dependence of autophosphorylation on Ca^{2+}; the Hill coefficient of the reaction was ~5. This marked dependence, which relied on the co-operative binding of Ca^{2+} to calmodulin and on the binding of Ca^{2+}/calmodulin to two separate CaMKII subunits, probably helps the enzyme to activate fully within the range of Ca^{2+} concentrations that occur at the synapse.

Remarkably, if they included purified PP1 in the reaction, they found an even steeper dependence on Ca^{2+}, with a Hill coefficient of ~8. In other words, CaMKII can go from a dephosphorylated state to a highly autophosphorylated state in response to tiny changes in Ca^{2+} levels. This implies that, in the presence of PP1 activity, CaMKII might remain dephosphorylated in response to small increases in Ca^{2+} (such as those that elicit LTD), but might strongly autophosphorylate in response to larger elevations (such as those that elicit LTP).

Bradshaw *et al.* also found that the phosphorylated state of the enzyme was reversible after the concentration of Ca^{2+} was reduced; that is, the reaction did not behave as a bistable switch. However, CaMKII is extraordinarily enriched at the synapse, and its interaction with PP1 is necessarily affected by the presence of numerous additional proteins. It is therefore probable that the switch behaves differently *in situ* than in the test tube. A new challenge is to determine whether the steep dependences that are reported in this study can be found at the synapse.

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References and links

ORIGINAL RESEARCH PAPER Bradshaw, J. M. *et al.* An ultrasensitive Ca^{2+}/calmodulin-dependent protein kinase II–protein phosphatase 1 switch facilitates specificity in postsynaptic calcium signaling. *Proc. Natl Acad. Sci. USA* **100**, 10512–10517 (2003)

FURTHER READING Lisman, J. *et al.* The molecular basis of CaMKII function in synaptic and behavioural memory. *Nature Rev. Neurosci.* **3**, 175–190 (2002)