

**Memory Mechanisms: Modifiability and Stability**

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We have made rapid progress towards the understanding of CaMKII in synaptic memory. One line of work has been theoretical, dealing with the stability of a CaMKII switch. Such stability issues are critical to evaluating this mechanism as a memory storage device. Previous work has established that a chemical system composed of CaMKII and Protein Phosphatase 1 could have two stable states, however the lifetime of these states must be limited by stochastic fluctuations. Using Monte-Carlo simulation, we examine how stability varied with number of molecules in the switch. Our key finding is that realistic numbers (<20) can retain the "on" or "off" state for many years without a spontaneous transition and could thus serve as a useful memory device. In a second line of theoretical work, we examined the role of neurogranin, a calmodulin buffer. Our simulations reproduce experiment showing that knockout of neurogranin blocks LTP, but not LTD. These simulations indicate that what neurogranin is doing is to provide a local source of calmodulin sufficient to bind to the high concentration of CaMKII that must be activated during LTP. A critical question is whether CaMKII is indeed a molecular memory. Experimental work with CaMKII inhibitors is now providing strong support for this hypothesis. We had also hoped to reconstitute the CaMKII switch in a test tube, but this has been problematical because of technical difficulties (noise in the biochemical assay). An additional goal of understanding the factors that control synapse and make size stable is just underway.

**Publications**

P. Miller, A. M. Zhabotinsky, J. E. Lisman, X.-J. Wang, The stability of a stochastic CaMKII switch: dependence on the number of enzyme molecules and protein turnover, *PloS*, **In press**. (2005).