Progress in Understanding the Molecular Basis of Memory

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Previous work using LTP as a model of memory pointed to the critical role of CaMKII as a molecular memory at CA1 hippocampal synapses. Roger Nicoll showed that perfusion of activated CaMKII into CA1 pyramidal cells saturated LTP. Moreover, in what is called the occlusion test, Nicoll showed that once saturated in this way, synapses could no longer undergo activity-dependent LTP. A second important test of a putative memory mechanism is the "erasure test". In work from my laboratory, we performed the erasure test using a permeable peptide (tat-CN21) known to interfere with CaMKII function. After inducing LTP we transiently applied this peptide. The results showed that this procedure produced a persistent erasure of saturated LTP. Moreover, after such erasure, LTP could be reinduced. The molecular switch that maintains LTP had thus been successfully reset. When CaMKII is activated during LTP induction, it binds to NMDARs in the activated spine. Tat-CN21 interferes with this binding. We therefore suspect that molecular memory is actually the complex of CaMKII with the NMDAR, a local complex that can underlie the synapse specificity of LTP.

We have now also performed the critical erasure test at the behavioral level. We used a virally expressed dominant negative form of CaMKII (K42M). Because the erasure test requires *transient* interference with CaMKII, we used HSV virus as a delivery system; this virus results in protein expression for only for a few days. Rats first underwent training in a place aversion task. We then virally expressed dominant negative CaMKII. Seven days later, we tested memory retention and found a strong deficit. This was not due to hippocampal damage, as rats could relearn. Thus, the dominant negative CaMKII had erased a behaviorally defined memory.

To be plausible as a storage mechanism for the engram, there must be molecular mechanisms that insure long-term stability of stored information. I will review recent data suggesting that the particular autophosphorylation properties and subunit exchange properties of CaMKII provide an elegant solution to the stability problem.

Finally, I will address the question of how synapses can modify their structure in a *graded* way to encode long-term memory. We estimate that synapses can have about 10 size states, allowing 3 bits of information storage. A potential mechanism for such gradation is simply to vary the number of bistable CaMKII switches.