The molecular mechanisms of memory persistence: remodeling of dendritic spine substructures during long-term potentiation and depression

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Memories are stored in the brain through the ability of each individual synapse to modify its molecular composition in a persistent and specific way. The precise chronology of these changes, however, has yet to be observed at subcellular resolution in a single synapse in real time.

We used a combination of optical technologies to reveal the molecular reorganization that takes place inside a dendritic spine during the induction of long-term potentiation (LTP) and depression (LTD). We stimulated single spines in hippocampus by two-photon glutamate uncaging and visualized postsynaptic protein trafficking in real time. We found several surprising and contradictory phenomena: 1) An actin-depolimerization factor was the only protein to be rapidly and persistently enriched at potentiated synapses, where it formed a new stable macromolecule that could serve as a memory tag. 2) The enlargement of the postsynaptic density was not synchronized with the LTP-associated spine enlargement, but one hour delayed. To confirm it, we developed a novel photo-marking technique that allowed us to localize the same spine under both two-photon and electron microscopies. 3) Spine shrinkage was associated with NMDA receptor-dependent LTD in a protein synthesis-dependent way, but not associated with metabotropic glutamate receptor-dependent LTD.

These findings may represent the molecular explanations for known phenomena of metaplasticity such as synaptic lability, saturation and tagging.