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Memory and Theseus' Ship: How Postsynaptic KIBRA Targets PKMzeta to Maintain Long-Term Memory

Memories are thought to be maintained by molecules that persistently enhance activated synaptic connections in neuronal networks. But memories can last much longer than synaptic proteins, whose lifespans are typically hours to days. How short-lived synaptic proteins can maintain long-term memory is unclear. Autonomously active kinases, such as the PKC isoform PKMzeta, act as "memory molecules" during long-term potentiation (LTP) by maintaining potentiated synaptic transmission at activated synapses. Here we show KIBRA, a postsynaptic scaffolding protein genetically linked to human memory performance, persistently anchors PKMzeta function to these activated synapses. Strong synaptic activation drives KIBRA and newly synthesized PKMzeta to postsynaptic sites, forming KIBRA-PKMzeta complexes that persist in late-LTP maintenance. To test the function of the complexes in LTP and memory maintenance, we decoupled KIBRA from PKMzeta by an antagonist of the KIBRA-binding site in PKMzeta and, conversely, by an antagonist of PKMzeta-binding in KIBRA. Neither antagonist measurably affects basal synaptic transmission. However, both decoupling agents reverse established late-LTP maintenance. Thus, KIBRA-PKMzeta coupling acts exclusively at activated synapses. Both agents erase spatial memory maintenance. Therefore, long-term memory is maintained by two interacting mechanisms: 1) persistent synaptic potentiation by PKMzeta, and 2) persistent anchoring of this action to activated synapses by KIBRA. While the sites of their interaction at activated synapses are stable, individual KIBRA and PKMzeta molecules within complexes are exchangeable. Thus, analogous to Theseus' Ship that was maintained despite continual replacement of its component parts, long-term memories are maintained by continual KIBRA-PKMzeta interactions despite the turnover of individual molecules.