Research uncovers 'molecular glue' that helps ensure memory formation and stabilization

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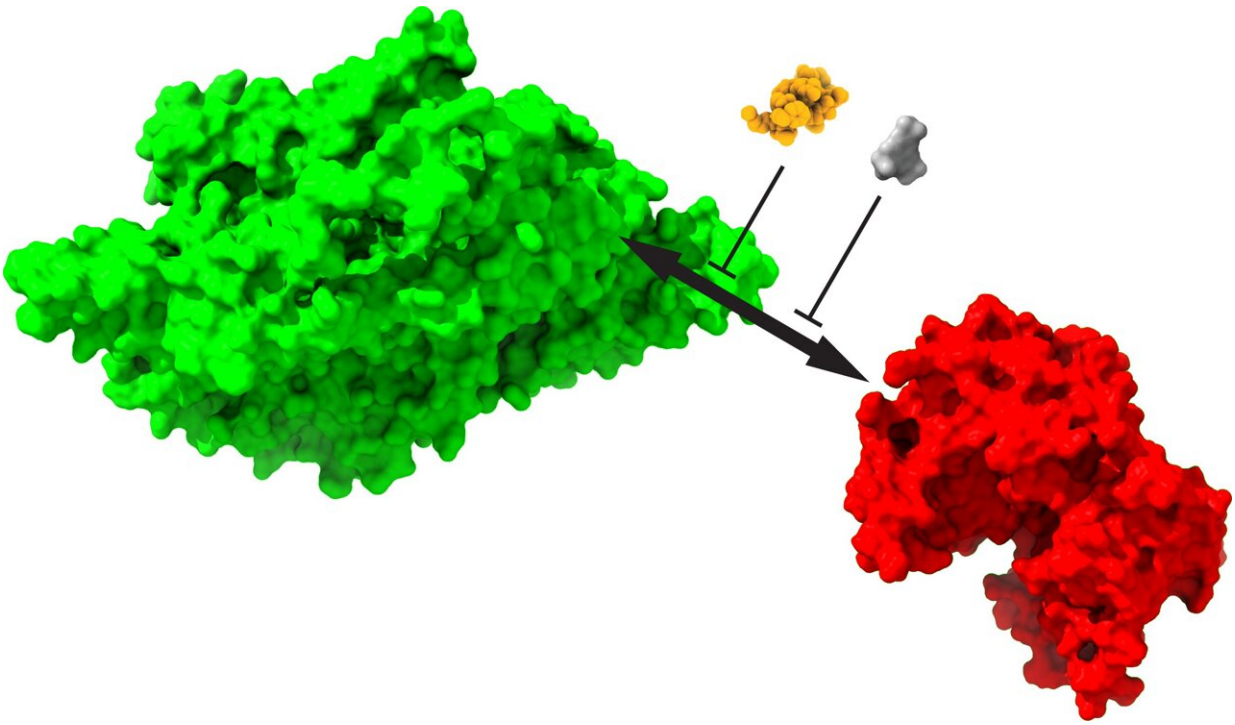

Memories are stored by the interaction of two proteins: a structural protein, KIBRA (green), that acts as a persistent synaptic tag, and a synapse-strengthening enzyme, protein kinase Mzeta (red). Drugs that disrupt the memory-perpetuating interaction (other colors) erase pre-established long-term and remote memories. Credit: Changchi Hsieh, Ph.D.

Whether it's a first-time visit to a zoo or when we learned to ride a bicycle, we have memories from our childhoods kept well into adult

years. But what explains how these memories last nearly an entire lifetime?

A study in the journal *Science Advances*, conducted by a team of international researchers, has uncovered a biological explanation for long-term memories. It centers on the discovery of the role of a molecule, KIBRA, that serves as a "glue" to other molecules, thereby solidifying memory formation.

"Previous efforts to understand how molecules store long-term memory focused on the individual actions of single molecules," explains André Fenton, a professor of neural science at New York University and one of the study's principal investigators. "Our study shows how they work together to ensure perpetual memory storage."

"A firmer understanding of how we keep our memories will help guide efforts to illuminate and address memory-related afflictions in the future," adds Todd Sacktor, a professor at SUNY Downstate Health Sciences University and one of the study's principal investigators.

It's been long-established that neurons store information in memory as the pattern of strong synapses and weak synapses, which determines the connectivity and function of neural networks. However, the molecules in synapses are unstable, continually moving around in the neurons, and wearing out and being replaced in hours to days, thereby raising the question: How, then, can memories be stable for years to decades?

In a study using laboratory mice, the scientists focused on the role of KIBRA, or kidney and brain expressed protein, the human genetic variants of which are associated with both good and poor memory. They focused on KIBRA's interactions with other molecules crucial to memory formation—in this case, protein kinase Mzeta (PKMzeta). This enzyme is the most crucial molecule for strengthening normal

mammalian synapses that is known, but it degrades after a few days.

Their experiments reveal that KIBRA is the "missing link" in long-term memories, serving as a "persistent synaptic tag," or glue, that sticks to strong synapses and to PKMzeta while also avoiding weak synapses.

"During memory formation the synapses involved in the formation are activated—and KIBRA is selectively positioned in these synapses," explains Sacktor, a professor of physiology, pharmacology, anesthesiology, and neurology at SUNY Downstate. "PKMzeta then attaches to the KIBRA-synaptic-tag and keeps those synapses strong. This allows the synapses to stick to newly made KIBRA, attracting more newly made PKMzeta."

More specifically, their experiments in the *Science Advances* paper show that breaking the KIBRA-PKMzeta bond erases old memory.

Previous work had shown that randomly increasing PKMzeta in the brain enhances weak or faded memories, which was mysterious because it should have done the opposite by acting at random locations, but the persistent synaptic tagging by KIBRA explains why the additional PKMzeta was memory enhancing, by only acting at the KIBRA tagged sites.

"The persistent synaptic tagging mechanism for the first time explains these results that are clinically relevant to neurological and psychiatric disorders of memory," observes Fenton, who is also on the faculty at NYU Langone Medical Center's Neuroscience Institute.

The paper's authors note that the research affirms a concept introduced in 1984 by Francis Crick. Sacktor and Fenton point out that his proposed hypothesis to explain the brain's role in memory storage despite constant cellular and molecular changes is a Theseus's Ship

mechanism—borrowed from a philosophical argument stemming from Greek mythology in which new planks replace old ones to maintain Theseus's Ship for years.

"The persistent synaptic tagging mechanism we found is analogous to how new planks replace old planks to maintain Theseus's Ship for generations, and allows memories to last for years even as the proteins maintaining the memory are replaced," says Sacktor.

"Francis Crick intuited this Theseus's Ship mechanism, even predicting the role for a protein kinase. But it took 40 years to discover that the components are KIBRA and PKMzeta and to work out the mechanism of their interaction."

The study also included researchers from Canada's McGill University, Germany's University Hospital of Münster, and University of Texas Medical School at Houston.

More information: Panayiotis Tsokas et al, KIBRA anchoring the action of PKMζ maintains the persistence of memory, *Science Advances* (2024). DOI: 10.1126/sciadv.adl0030.
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