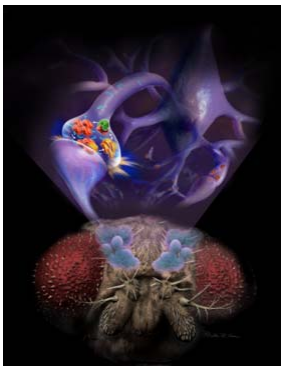
Prions Are Key to Preserving Long-term Memories

The famed protein chain reaction that made mad cow disease a terror may be involved in helping to ensure that our recollections don't fade
Feb 18, 2014 |By Beth Skwarecki / Scientific American



A protein called Tob (*green*) binds and allows another protein, monomeric Orb2A (*red*) to persist intact in a neuron and thereby enable a chain reaction to maintain a permanent memory. *Credit: Nicolle Rager Fuller, Sayo-Art*

Prions, the protein family notorious for causing "mad cow" and neurodegenerative diseases like Parkinson's, can play an important role in healthy cells. "Do you think God created prions just to kill?" mused Nobel laureate Eric Kandel. "These things must have evolved initially to have a physiological function." His work on memory helped reveal that animals make and use prions in their nervous systems as part of an essential function: stabilizing the synapses that constitute long-term memories. These natural prions aren't infectious but on a molecular level they chain up exactly the same way as their disease-causing brethren. (Some researchers call them "prionlike" to avoid confusion.) This week, work from neuroscientist Kausik Si of the Stowers Institute for Medical Research, one of Kandel's former students, shows that the prion's action is tightly controlled by the cell, and can be turned on when a new long-term memory needs to be formed.

Prions are proteins with two unusual properties: First, they can switch between two possible shapes, one that is stable on its own and an alternate conformation that can form chains. Second, the chain-forming version has to be able to trigger others to change shape and join the chain. Say that in the normal version the protein is folded so that one portion of the protein structure—call it "tab A"—fits into its own "slot B." In the alternate form, though, tab A is available to fit into its *neighbor's* slot B. That means the neighbor can do the same thing to the next protein to come along, forming a chain or clump that can grow indefinitely.

The clumps produced in prion diseases are toxic to the cell but certain other protein chains have a role in healthy neurons. Their self-propagating chain reactions are the solution to a dilemma the cell faces: how to maintain a permanent memory when the set of cellular processes that formed the memory are long completed Or, as Si puts it, "How

can you create a permanent state with molecules that are going to disappear within two months?"

For a brain cell, keeping a memory around is a lot of work. A variety of proteins need to be continually manufactured at the synapse, the small gap that interfaces one cell to another. But whereas a cell may have a multitude of synapses, the protein synthesis that grows and maintains the connection only occurs at specific ones that have been activated. Work in the sea slug *Aplysia* (a favorite of neuroscientists because of its large cells) showed that a protein called CPEB, for cytoplasmic polyadenylation element binding, is necessary to keep a synapse activated. Si and Kandel, working with yeast prion specialist Susan Lindquist of the Massachusetts Institute of Technology, showed in 2003 that CPEB acts as a prion.

Once the prion's chain reaction gets started it's self-perpetuating, and thus the synapse can be maintained after the initial trigger is gone—perhaps for a lifetime. But that still doesn't explain how the first prion is triggered or why it only happens in certain synapses and not others.

An answer comes from Si's work on fruit flies, published February 11 in *PLoS Biology*. Sex—and, in particular, male courtship behavior—is an ideal realm in which to test memory: If a female is unreceptive, the male will remember this and stop trying to court her. Earlier, Si's team showed that if the fly's version of CPEB, called Orb2, is mutated so that it cannot act as a prion, the insect briefly remembers that the female is unreceptive but that memory fades over the course of a few days.

Now, Si's team has figured out how the cell turns on the machinery responsible for the persistence of memory—and how the memory can be stabilized at just the right time and in the right place.

Before the memory is formed a fly's neuron is full of a version of the prion called Orb2B. Although this version can switch shapes to form prions' characteristic clumps, it can't get started without the related protein Orb2A. In this week's paper Si and colleagues untangled the multipartnered dance that controls Orb2A's role. First, a protein called TOB binds to Orb2A, allowing it to persist intact in the cell. (Normally, it would be broken down within a few hours.) Once stabilized it needs to have a phosphate tag attached, and this is done by another protein called Lim kinase.

Crucially, Lim kinase is only activated when the cell receives an electrical impulse—and only targeted at that synapse, not any other synaptic connections the cell might also be making. That means that the prion chain reaction is turned on in the specific time and place it's needed. This, researchers say, means the cell has a mechanism to stabilize some synapses but not others—potentially explaining why some of our memories fade, whereas others last a lifetime.

Although work so far on these proteins has been in yeast, sea slugs, flies and mice, the human CPEB may operate in the same way to preserve memories. The next steps, both

researchers agree, are to develop better techniques to see where in the brain prions are activated, and to dig into more questions about how the prion process is regulated. One burning question: When we forget, does that mean that the prion's chain reaction has been halted?