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Weakening synapses to cull memories:

Calcium sensor synaptotagmin-3 helps weaken synaptic strength and supports forgetting

Nataniel J. Mandelberg and Richard Tsien

Langone Medical Center, New York University, New York, NY, USA

From correct answers on a school exam to a loved one's birthday, we have all forgotten things we wish we had not. The ability to forget, however, is a feature rather than a flaw of how our brains work. As the celebrated author Jorge Luis Borges wrote about a man incapable of forgetting, *Funes the Memorious* (1), "I suspect, however, that he was not very capable of thought. To think is to forget differences, generalize, make abstractions." Although Funes's example is literary, it contains a grain of truth. Neuroscientists have traditionally paid more attention to how the brain remembers than how it forgets, but there is increasing clarity about mechanisms and roles of forgetting (2, 3). By forgetting, we prioritize and separate the useful from the irrelevant and more easily reorganize information to learn (4). On page 44 of this issue, Awasthi *et al.* (5) show that the Ca^{2+} -sensing protein synaptotagmin-3 (SYT3) is essential for synaptic weakening and link this molecular process to beneficial forgetting in mice.

A compelling association exists between memory and changes in neuron connectivity. Neurons are linked by synapses, structures in which boutons from the axon of the upstream (presynaptic) neuron communicate with spines on dendrites of the downstream (postsynaptic) neuron via neurotransmitter release. If the presynaptic neuron reliably drives the activity of the postsynaptic neuron, the synapse's strength, or weight, increases through long-term potentiation (LTP). However, if the activities of the neurons are poorly correlated, the connection weakens through long-term depression (LTD). Controlling LTP and LTD in rodents drastically affects memories they have formed: Previously learned fear conditioning in mice can be deactivated through optogenetically induced LTD and reactivated with LTP (6). LTP occurs when the activity of the presynaptic neuron causes a large influx of Ca^{2+} into the postsynaptic neuron. It manifests as an increased number of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type 2 subunit-containing glutamate (GluA2) receptors at the spine, making the postsynaptic neuron more responsive to input from the presynaptic cell. By contrast, LTD is driven by smaller Ca^{2+} events and reflects the removal of GluA2 receptors from the synapse through endocytosis, weakening the connection.

To clarify the mechanism of GluA2 receptor endocytosis, Awasthi *et al.* looked closely at members of the synaptotagmin family of Ca^{2+} -sensitive proteins. Synaptotagmins control the exocytosis of presynaptic vesicles (full of neurotransmitters) from the bouton, and postsynaptic SYT1 and SYT7 are required for glutamate receptor exocytosis in LTP (7). Awasthi *et al.* show that SYT3 has key qualifications to be the arbiter of LTD through its

regulation of GluA2 receptors: SYT3 is abundant at postsynaptic regions, is endocytosed when neurons are stimulated, binds directly to GluA2 receptors, and controls their internalization. Awasthi *et al.* show that SYT3 has a functional impact on synaptic plasticity. Induction of LTP was unaffected by *Syt3* gene deletion in mice, whereas the decay of LTP and the induction of LTD, both reliant on GluA2 receptor endocytosis, were abolished.

Notably, SYT3 binds Ca^{2+} at 5- to 20-fold lower concentrations (8) than does SYT1, which participates in postsynaptic recruitment of GluA2 receptors in LTP (7). Taken together, these findings (5, 7, 8) align with a model that attributes the different Ca^{2+} requirements of LTP and LTD to their structurally divergent Ca^{2+} sensors. Other players, such as calmodulin kinases and calcineurin, may also participate in the all-important molecular decision between synaptic strengthening and weakening. Work is needed to further integrate postsynaptic vesicle cycling and signaling biochemistry.

Awasthi *et al.* show that these circuit-level findings have in vivo relevance by training mice to find target locations. When *Syt3* was deleted, the mice learned the target location as well as the wild-type mice did but, when the target was moved, showed impaired forgetting of the initial location, reflected by an unwillingness to leave the target's original location. These results extend reports that GluA2 receptor endocytosis mediates memory loss (9) and that blocking this endocytosis preserves memories (10), by showing that this process is mediated by SYT3 in vivo.

Awasthi *et al.* go on to demonstrate that this inability to forget hinders behavioral flexibility, much as in Borges's story of Funes. The mice were again tasked with finding a hidden platform in a pool of water, but the location of the platform was changed every day. Mice in which *Syt3* was deleted persisted with former platform locations rather than seeking new ones, as if unable to distinguish between a past memory and a new, immediately relevant experience.

The study of Awasthi *et al.* highlights the importance of vesicle cycling on both sides of the synapse. Clarification of the cell biology of how postsynaptic weights are weakened shifts the spotlight to questions about the spatiotemporal allocation and reallocation of such weights. We speculate that the internalized glutamate receptor vesicles are a synaptic resource too precious to waste and can be redistributed among nearby dendritic spines to strengthen nearby postsynapses (11), much as vesicles of neurotransmitters can be reallocated among presynaptic boutons along an axon (12). This study begins to show how neurons might use similar tools pre- and postsynaptically to channel resources to the most important synapses while culling synapses that no longer encode relevant information.

The work of Awasthi *et al.* has a close yet unexplored relationship to pathological processes in neuropsychiatric and neurodegenerative disorders. The exaggerated removal of glutamate receptors, including GluA2 receptors, is a feature of Alzheimer's disease (AD) (13) and potentially linked to the associated forgetting. This process involves protein interacting with C kinase-1 (PICK1), another mediator of GluA2 receptor endocytosis (14), but the role of SYT3 and the relationships between PICK1, SYT3, and other proteins involved in GluA2 receptor endocytosis remain unclear. This pathophysiological endocytosis could contribute

to the memory loss experienced by AD patients, and we speculate that pharmacological interventions that restore normal GluA2 receptor endocytosis could help mitigate these defects. Furthermore, behavioral inflexibility is a hallmark of autism spectrum disorders (ASD) and might be assigned to deficits in forgetting, as supported by five fruitfly models of ASD risk genes (2). In another study, patients with ASD were asked to choose the location of a stimulus. Although they performed equally well as the control patients, the ASD patients showed extra reversion back to the original location even after the stimulus location changed (15). Elucidation of mechanisms of this inflexibility will benefit from the insights that Awasthi *et al.* have elegantly provided. ■

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Switching between remembering and forgetting

In this model, different SYT isoforms with different Ca^{2+} affinities (8) determine whether GluA2 receptors should be added to synapses, which strengthens them (LTP), or removed, which weakens them (LTD). This contributes at the synaptic level to the decision in the brain of whether a memory should be encoded or forgotten.