"I'VE A GRAND MEMORY FOR FORGETTING": THE NEURAL BASIS OF MEMORY & FORGETTING

SUSANNA L. CUNNINGHAM, HELEN T. BUCKLAND, JENNY L. WILLIAMSON

> "I've a grand memory for forgetting."
>
> —Robert Louis Stevenson

In last month's column, we defined "learning" and described the basic functional elements of the nervous system used in learning. The ability to learn is a critical survival skill. Although neuroscience cannot explain all aspects of learning and memory, many basic processes are understood. Among them is synaptic plasticity, the focus of this column.

Synaptic plasticity underlies our ability to remember and forget – by either strengthening or weakening synapses. Synaptic plasticity involves two components: long-term potentiation (LTP), important for strengthening memory, and long-term depression (LTD), which weakens memory and leads to forgetting. Long-term potentiation is "a long-lasting increase in the efficacy of transmission at excitatory synapses," whereas LTD is a long-lasting decrease in efficacy (Blaustein et al., 2012). LTP occurs where there is an increase in activity at a synapse: LTD occurs when there is lessened activity. Memory involves changes in the presynaptic cell membrane and post-synaptic receptors, as well as the creation of new proteins and an increase in dendritic spines' size and density (Blundon & Zakharenko, 2008).

Bliss and Lomo (1973) did the experimental work that described long-term potentiation. Current work indicates that some mechanisms underlying LTP vary depending on brain region. In the hippocampus, the area associated with learning and memory, LTP occurs in two steps. The first step occurs rapidly after a neuron is stimulated, and the second step takes hours to develop (Blundon & Zakharenko, 2008).

One rapid step that is a component of LTP is the stimulation of excitatory synapses in the hippocampus, triggering release of the neurotransmitter glutamate. Glutamate diffuses across the synaptic cleft and binds to two key glutamate receptors, NMDA receptors (NMDARs) and AMPA receptors (AMPARs). These receptors were named for the two pharmaceutical chemicals that block them, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA). For an animation of the role of these receptors in glutaminergic transmission at synapses, see http://www.sumanasinc.com/webcontent/animations/content/receptors.html.

A second rapid step occurs when glutamate binds to the AMPA receptor, and the post-synaptic membrane begins to depolarize. This depolarization leads to activation of NMDA receptors because depolarization displaces magnesium ions that block the ion channels on the NMDARs. Calcium ions then flow into the post-synaptic dendritic spines. Incoming calcium ions bind to calmodulin and activate a protein kinase. Activation of this kinase leads to (1) phosphorylation of AMPARs, increasing their conductance and the depolarization of the post-synaptic cell; and (2) insertion of AMPARs into the post-synaptic membrane, further supporting depolarization and "strengthening" the synapse.

The later step of LTP involves gene transcription and new protein synthesis at the synapse. New research indicates that brain-derived neurotrophic factor (BDNF), key in embryonic development, has a role in memory. BDNF influences several mechanisms that increase glutamate release during LTP. One of these mechanisms is an increase in the expression of vesicular glutamate receptor 1 (VGLUT1). VGULT1 loads glutamate into the presynaptic vesicles carrying glutamate to the presynaptic membrane, and also increases the number of synaptic vesicles that dock at the active area of the presynaptic membrane (Melo et al., 2013).

LTD occurs when a synapse receives weak or diminished input. Consider what typically happens when you change your address; neurons involved in remembering your earlier address will no longer be activated. As their input decreases, synapses undergo LTD, and your ability to retrieve your old address wanes over time. When a synapse has decreased input, a series of changes results in the dephosphorylation of the AMPA receptors that were phosphorylated in LTP. A calcium-dependent phosphatase, calcineurin, causes this dephosphorylation. Calcineurin activates a second phosphatase, protein phosphatase 1, key in removing AMPARs from the post-synaptic membrane, reducing responsiveness to incoming signals (Blaustein et al., 2012).

It is interesting to note that both LTP and LTD are dependent on calcium influx into the post-synaptic dendritic spine. It is thought that differences in the time course of the calcium release allow one type of signal to result in two opposing outcomes.

Next month's article will focus on an important precursor to memory – attention. Get ready to pay attention as we find out how our brains hone in on what we perceive as important. Without attention, learning would not have a chance!

Acknowledgments

This project was funded by the National Institute on Drug Abuse, National Institutes of Health, under award no. R25DA028796. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

Blaustein, M.P., Kao, J.P.Y. & Matteson, D.R. (2012). *Cellular Physiology and Neurophysiology, 2nd Ed.* Philadelphia, PA: Elsevier/Mosby.

Bliss, T.V. & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, *232*, 331–356.

Blundon, J.A. & Zakharenko, S.S. (2008). Dissecting the components of long-term potentiation. *Neuroscientist*, *14*, 598–608.

Melo, C.V., Mele, M., Curcio, M., Comprido, D., Silva, C.G. & Duarte, C.B. (2013). BDNF regulates the expression and distribution of vesicular glutamate transporters in cultured hippocampal neurons. *PLoS ONE*, *8*(1), e53793.

SUSANNA L. CUNNINGHAM is Professor at the University of Washington, School of Nursing, T618B Health Sciences, 1959 NE Pacific Street, Seattle, WA 98195-7266; e-mail: susannac@uw.edu. HELEN T. BUCKLAND is Project Director of Online Neuroscience Education about Drug Addiction at the University of Washington, School of Nursing, T610A Health Sciences, 1959 NE Pacific Street, Seattle, WA 98195-7266; e-mail: trezbuck@uw.edu. JENNY L. WILLIAMSON is the Project Director for How Do I Learn at the University of Washington, School of Nursing, T610A Health Sciences, 1959 NE Pacific Street, Seattle, WA 98195-7266. For questions about this article, please contact Jenny L. Williamson at jenlw@uw.edu.

The American Biology Teacher, Vol. 75, No. 7, page 503. ISSN 0002-7685, electronic ISSN 1938-4211.
DOI: 10.1525/abt.2013.75.7.11