NEUROSCIENCE: Enhanced: A Missing Link? LTP and Learning

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The search for changes in neurons and synapses that take place during learning has fascinated neuroscientists for decades. [HN2], [HN3] In 1973 Bliss and Lomo (1) made the remarkable discovery that communication between neurons across synapses in rabbit brain undergoes a long–lasting enhancement upon repeated electrical stimulation. This finding was especially satisfying because the changes occurred in the hippocampus, a part of the brain known to be important for memory, and because the patterns of stimulation included the types of neural activity that an animal might experience during learning. The phenomenon was subsequently called long–term potentiation (LTP) and has been intensely investigated ever since. Almost everyone in the field has assumed that LTP is a cellular correlate of learning—in part, because there are few other good candidates with the correct attributes. In spite of this almost universal assumption, there are precious few data directly linking LTP to learning. Have Murphy and Glanzman, on page 467 of this issue (2), provided this missing link? They certainly present some of the strongest evidence to date.

The Holy Grail of memory research is the elucidation of learning and memory at the cellular and molecular levels. There have been significant advances in this quest during the past year with the development of the ability to eliminate specific genes in a time- and location-specific manner in mice. In a beautiful series of papers that showed that elimination of two molecules known to be important for LTP [N–methyl–D–aspartate (NMDA) receptors and calcium–calmodulin–dependent protein kinase II [HN4]] from the hippocampus disrupts both LTP and learning in the Morris water maze (3). This maze requires hippocampal–dependent spatial learning as rats or mice swim in a tank of murky water to find a submerged platform (4). Because of the complexity of the behavior, however, the direct role of LTP in this learning paradigm is controversial (5). Nevertheless, these experiments are consistent with a strong connection between LTP and learning and are among the best data available in mammals.

Establishing a direct link between LTP and learning is hard to achieve in mammals. It is difficult to record from synaptic pathways during the actual behavior, and most behavioral tests of learning (including the Morris test) have complex sensory and motor components in which LTP might also play a role. Enter the simple–system approach to memory research—an approach that makes use of relatively primitive organisms, such as the marine invertebrate Aplysia, to investigate the underlying mechanisms of behavioral learning at single synapses.

Aplysia is a sea slug with many virtues: the large size of its neurons, its simple behaviors, and its ability to modulate those behaviors (learn) through a relatively simple nervous system. [HN7], [HN8] Thirty years ago, Kandel and his colleagues pioneered the use of Aplysia for memory research. Since then they have mapped much of its nervous system, documented several of its behaviors and the underlying neural circuitry, and established simple learning paradigms such as classical conditioning of the siphon and gill withdrawal reflex (6).

But with the discovery of LTP in the hippocampus of rabbits in 1973 and its intriguing candidacy as a substrate of memory, the simple system approach lost some of its luster. Why study a simple invertebrate system when there exists a “simple” synaptic plasticity in a higher organism that is likely involved in mammalian learning? It is ironic that the link between LTP and learning now reported by Murphy and Glanzman has come not from mammals, but from the more primitive Aplysia in which LTP has only recently been described.

Synapses in Aplysia exhibit short– and long–term synaptic plasticities that play different roles in behavior (7). In particular, synapses from sensory neurons onto the motor neurons that mediate withdrawal of the siphon are the site of learning during classical conditioning of the withdrawal reflex (8) (see the figure). In 1994, Lin and Glanzman (9) demonstrated an LTP–like plasticity at these sensorimotor synapses that depends on an NMDA–related receptor. NMDA receptors are a subclass of glutamate receptors that act as molecular coincidence detectors for pre– and postsynaptic activity and are responsible for LTP at many (but not all) synapses, including LTP at certain synapses in the hippocampus. The receptors open channels only when simultaneously there is neurotransmitter released from the presynaptic terminal and the postsynaptic neuron.
The opening of the channels, in turn, allows a flux of calcium ions into the postsynaptic neuron, initiating a series of poorly understood steps that either increase neurotransmitter release or increase the postsynaptic response to the transmitter. The NMDA receptors provide a molecular basis for the so-called Hebb postulate of learning. This notion, put forth in 1949 by the psychologist Hebb, states that learning is mediated by changes in synaptic strengths when there is conjunctive firing of pre- and postsynaptic neurons. The finding of NMDA receptors and NMDA receptor–dependent LTP at Aplysia sensorimotor synapses was significant for two reasons. First, it demonstrated that there is a postsynaptic component to long–term plasticity at perhaps the only synapse where LTP was universally thought to involve presynaptic and non–Hebbian mechanisms. Second, it suggested to Glanzman the use of the common NMDA receptor antagonist D,L–2–amin o–5–phosphonovaleric acid (APV) to test for a link between LTP and learning in an invertebrate nervous system.

Murphy and Glanzman now show that classical conditioning of the synaptic response from sensory neurons to motor neurons is blocked by APV (see the figure). Furthermore, APV has no effects on nonassociative learning or on other facilitatory pathways that might also contribute to aspects of the behavior. Thus, the associative properties of the NMDA receptor are required for associative conditioning. Although this classical conditioning of the synaptic pathway is known to mediate the behavior of siphon withdrawal, an effect of APV on the learning of the behavior in the animal has not yet been shown. This will clearly be the next step.

The experiments described by Murphy and Glanzman provide an important test of the hypothesis that LTP–like synaptic plasticity mediates learning in a simple, well–defined task in a simple, well–defined neural circuit. It strengthens the link between Hebbian plasticity and associative learning and suggests a conservation of mechanisms among evolutionarily diverse organisms such as sea slugs and mammals. Hence, some further confidence is provided for those holding the belief that LTP equals memory.

References


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HyperNotes

Related Resources on the World Wide Web

General Hypernotes

The University of Alberta's Cognitive Science Dictionary defines long–term potentiation and other terms used in this Perspective.

Neuroscience Web Search, developed at the Baylor University College of Medicine, allows users to search the Web for topics in neuroscience. The page also lists other neuroscience resources on the Web.

A Brief Tour of the Brain, developed at Syracuse University, describes the structure of the brain and the anatomy of neurons. Large Scale Features describes the hippocampus, and Building Blocks describes neurons and synapses.

The World Wide Web Virtual Library Neuroscience (Biosciences), one component of the World Wide Web Virtual Library, provides an extensive list of links to journals, books, software, laboratory Web pages, and other resources in the neurosciences. The World Wide Web Virtual Library Psychology lists Web resources in psychology and behavioral sciences including learning and memory.

The Whole Brain Atlas, developed at Harvard University, provides CT and MRI images of the human brain with the names of structures indicated.

Neurosciences on the Internet is an index of Internet neuroscience resources that also publishes original material in all areas of the neurosciences. The site is edited and maintained by Neil A. Busis.

Neuroscience for Kids, maintained by Eric H. Chudler at the University of Washington, is designed for elementary and secondary school students and teachers who would like to learn more about the nervous system. It includes descriptions of experiments and diagrams, and explanations and diagrams of neuroanatomical structures, and links to other sites of interest.

Cognitive and Psychological Sciences on the Internet is an index to Internet resources relevant to research in cognitive science and psychology.

Numbered Hypernotes

2. The Biological Neuron provides schematic illustrations of the neuron and the synapse. The Biological Neuron is a component of Neil's Neural Nets, a site maintained at Carleton College that describes the basic elements of neural networks.
1. **Memory: A Glimpse into the Past, an Understanding of the Present, and a Key to the Future** by Melody Desing covers the neurophysiology and anatomy of memory and describes the work of D. O. Hebb.

1. **Eric R. Kandel's** Web page at Columbia University describes his research and lists selected publications.

1. **Susumu Tonegawa's Web page at the Howard Hughes Medical Institute** describes his research. **Tonegawa's Web page at MIT** summarizes his research interests and lists selected publications.

1. **Calcium-Calmodulin Dependent Protein Kinase II** describes the structure and function of calcium-calmodulin dependent protein kinase II in *Drosophila*. This page is a part of the **Interactive Fly**, a guide to *Drosophila* genes and their roles in development.

1. **Aplysia: a Simple System** provides descriptions of *Aplysia*, its gill-withdrawal reflex, classic conditioning, and the neurophysiology of memory in *Aplysia*.

1. **The Aplysia Hometank** is the Web site of the *Aplysia* Database Project. The *Aplysia* database will contain descriptions of identified and identifiable neurons, actual data sets of neurophysiological data from both identified cells and candidates for neuronal identification, and model parameters useful for electrophysiological simulations of neurons and networks.

1. **The Hebbian learning rule** is defined in the University of Alberta's **Cognitive Science Dictionary**.

1. **Lecture 27: Learning and Memory** by R. Meldrum Robertson describes Hebb's postulate.