NEUROSCIENCE

A Missing Link? LTP and Learning

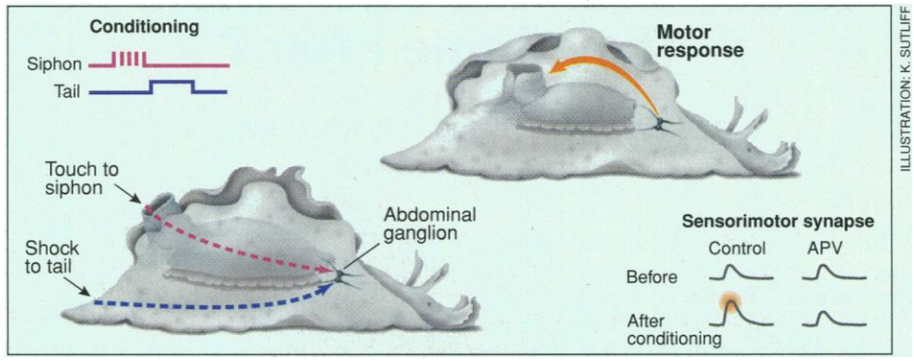
Dan Johnston

The search for changes in neurons and synapses that take place during learning has fascinated neuroscientists for decades. 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 represented a watershed of sorts for the field, the laboratories of Tonegawa at the Massachusetts Institute of Technology and Kandel at Columbia University 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] 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.

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 is depolarized. 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 (*10*). The finding of NMDA receptors (*11*) and NMDA receptor–dependent LTP at *Aplysia* sensorimotor synapses (*9*) 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



Simple learning and LTP. In the marine mollusk *Aplysia* the siphon withdrawal reflex can be enhanced by repeatedly pairing weak siphon touch with tail shock. After this classical conditioning, the withdrawal reflex from siphon touch is enhanced through an APV-sensitive LTP at the sensorimotor synapse.

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. 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.

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use of the common NMDA receptor antagonist D,L-2-amino-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.

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NEUROSCIENCE

Neocortical Neurons: Where Do They Come From?

Andrew Lumsden and Massimo Gulisano

The neocortex develops from an unpromising pair of bulges at the anterior end of the neural tube. The thin dorsal wall of each of these telencephalic vesicles produces the neocortex, whereas a bulbous swelling of the ventral wall produces the striatum—a component of the basal ganglia that receives major input from the neocortex (see the figure). Early in telencephalic morphogenesis, a prominent junction appears between the neocortical and striatal regions. Because this junction coincides with the borders of regulatory gene expression domains (*1*) and appears to segregate cells with markedly different fates (*2*), it is thought of as a boundary that partitions the telencephalon into discrete, developmentally independent compartments (*3*). Thus, the textbook view is that neocortical neurons originate exclusively from precursors that are contained within neocortical proliferative zones. This view is now challenged by Anderson *et al.* (*4*) on page 474 of this issue. They describe the origin of a subpopulation of neocortical interneurons from the developing striatum, implying that these cells migrate across the supposedly cell-tight corticostriatal junction. Significantly, this migration fails when two homeodomain transcription factors normally expressed by striatal precursor cells, DLX-1 and DLX-2, are deleted by gene targeting.

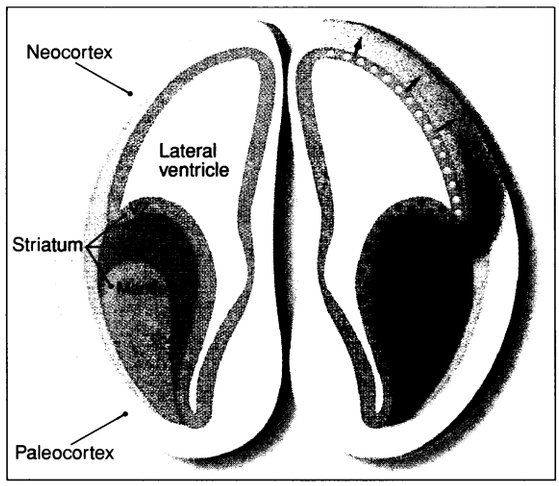

ILLUSTRATION: K. SUTLIFF

The telencephalon of an embryonic mouse. On the right, *Dlx-1*– and *Dlx-2*–expressing cells of the striatal VZ and SVZ (red) migrate into the striatal mantle and into the neocortex (arrows), where they mix with the radially migrating descendants of cortical precursors (yellow). Regions of the embryonic day 14 telencephalon shown on the left.

Most forebrain neurons are produced directly from the germinative epithelium of the ventricular zone (VZ), although some later-born neurons arise indirectly from the VZ by means of a secondary proliferative population (SPP) of nonepithelial cells that congregate in the subventricular zone (SVZ). As they differentiate, young neurons migrate out of the VZ and SVZ and into the subjacent mantle zone. Two members of the *Dlx* gene family, *Dlx-1* and *Dlx-2*, have virtually identical expression in these maturational zones of the striatum: Both genes are active (from embryonic day 9.5 in the mouse) in a subset of cells in the VZ and later in most cells of the SVZ, but the genes are switched off once the cells reach the mantle. Expression of *Dlx-1* and *Dlx-2* thus marks the transition from proliferation to differentiation (see the figure). One or the other of the genes is required for normal striatal histogenesis: In homozygous *Dlx-1/2* double knockout mice (but not in the single gene knockouts), partially differentiated neurons fail to migrate, piling up in the SVZ, and the mantle is depleted of late-born, SPP-derived neurons (*5*).

Dlx-1 and *Dlx-2* are not expressed in cortical proliferative zones, but immunopositive cells later turn up in the subventricular, intermediate, and marginal zones of the neocortex (*4*, *6*). Together with other data (*7*), these results suggested that striatal progenitors might also generate neocortical neurons—an intriguing possibility that has now been explored by Rubenstein and his colleagues (*4*). First, using vital dye labeling in slices of normal embryonic day 12.5 mouse forebrain, the authors found that cells marked in the striatal SVZ end up in the neocortex. Second, when the neocortical region is detached at its junc-

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