Neural Models Yield Data on Learning

A recent meeting on "Neural Models of Plasticity: Theoretical and Empirical Approaches" brought together the "wet nets"—experimental neurobiologists who study the neural bases for changes in animal behavior—and the "dry nets"—theoreticians who devise computational models to quantify and predict the biological phenomena. The inevitable marriage of the two approaches is revealing new information about changes within the nervous system that may underlie learning.*

Baby Snails Offer Clues to Adult Learning Skills

Aplysia, a sea mollusk that can learn to increase or decrease its reflex responses to certain stimuli, does not develop these skills all at once. Instead, different forms of learning emerge sequentially during its snail childhood and adolescence. Thomas Carew of Yale University and his co-workers have just identified when *Aplysia* acquires various learning skills and are now correlating specific changes in the nervous system with the acquisition of new learning capacities during development. Their data also refute a prevailing view about learning in adult snails.

Using different sets of stimuli, researchers can train an adult *Aplysia* to modify the withdrawal response of its siphon, a structure that controls respiration. Adult snails can increase the response (sensitization), decrease it (habituation), or increase a habituated response (dishabituation). Carew, Catherine Rankin, Thomas Nolen, Emilie Marcus, and Mark Stopfer, also of Yale, find that in baby *Aplysia*, the immature nervous system cannot carry out all the different forms of learning typical of the adult animal. Habituation develops first, then dishabituation, and finally sensitization.

"The idea is to use development in *Aplysia* as an analytical tool to relate specific kinds of nerve cells to specific forms of learning," says Carew. One of the most surprising findings in the new work is that, at developmental stage 11, when the baby snails are about 1.5 millimeters long, the animals can decrease the siphon-withdrawal response and then increase it from this decremented level, but not increase it from baseline. The sensitization process does not appear until about 60 days later in developmental stage 12.

This was a surprise because previous experiments with adult animals had led Carew, along with Eric Kandel and Vincent Castellucci of the Howard Hughes Medical Institute at Columbia University in New York and their colleagues, to conclude that sensitization and dishabituation were the same phenomenon. But Binyamin Hocner, also of Columbia, and Kandel recently reported data on cellular events in *Aplysia* that suggested the two phemonena are different, and Carew's new results on intact young animals support their findings.

Carew thinks that "at least three different processes occur during the development of the dishabituation process—the development of dishabituation itself, an inhibitory process that subtracts from it, and a sensitizing process that adds to it. When sensitization finally emerges, dishabituation doubles," he says.

David Cash, also of Yale, counted neurons in all the major ganglia of *Aplysia* at each developmental stage and found that they increase dramatically at about the same time as the sensitization process emerges. Carew suggests that the new work may point to a common signal that turns on the proliferation of nerve cells. "An interesting question is whether some component of the same signal also controls the onset of sensitization," he says. "And now that we know that simple forms of learning occur sequentially during development, we can begin to study when more complex forms of learning, such as classical conditioning, appear."

Hippocampus Studied for Learning Mechanisms

Almost by definition, learning means that changes must occur in the brain, and memory means that at least some of them must be stored. But how these events occur is still largely a mystery. Of the different changes in neuronal communication thought to underlie learning in the mammalian brain, perhaps the best understood occur in the hippocampus, a primitive part of the cerebral cortex.

Within the past year, researchers showed that postsynaptic nerve cells, which receive signals from presynaptic neurons across synapses, play a key role in the induction of long-lasting changes in communication in the hippocampus. But induction is only part of the picture. No one knows what makes the increased communication among nerve cells last, and this second challenge is where much of the current excitement lies.

In an attempt to mimic what may occur during certain forms of learning in the intact animal, researchers give brief trains of electrical stimuli to specific neural pathways in slices of hippocampus in vitro. This induces a long-lasting increase in the strength of synaptic connections, called long-term potentiation (LTP). Like many kinds of learning, LTP occurs quickly and persists.

"The induction of LTP requires both synaptic activity [neurotransmitter release from presynaptic neurons] and strong depolarization of the postsynaptic cell," says Tim Bliss of the National Institute for Medical Research in London. "You cannot get LTP without presynaptic activity, but the triggering event—the entry of calcium ions—is postsynaptic."

This critical participation of the postsynaptic neuron and the requirement that the electrical charge across its membrane must become more positive (depolarization) for LTP to be initiated is the new work of several groups led by Holger Wigström of the University of Göteborg in Sweden, Thomas Brown of the Beckman Research Institute of the City of Hope in Duarte, California, and B. Sastry of the University of British Columbia in Vancouver.

Two other research teams, headed by Gary Westbrook of the National Institute of Child Health and Human Development (NICHD) and Graham Collingridge of the University of British Columbia, described some of the molecular requirements for LTP. They found that, in most parts of the hippocampus, the induction of LTP seems to depend on the action of NMDA (*N*-methyl-D-aspartate) receptors, which are probably activated by the neurotransmitter glutamate in vivo. NMDA receptors control the activity of certain ion channels that allow calcium to pass through if the postsynaptic cell is sufficiently depolarized. The depolarization is necessary because it somehow dislodges magnesium ions that block the calcium-conducting ability of the ion channels, according to recent data from laboratories led by Phillipe Ascher of the Ecole Normale Supérieure in Paris and Mark Mayer, now of NICHD.

Researchers are still investigating specific

*"Neural Models of Plasticity: Theoretical and Empirical Approaches" was held 29 April to 1 May at the Marine Biological Laboratories in Woods Hole, Massachusetts.

roles that calcium plays in LTP and have already found that it probably activates enzyme-mediated processes within postsynaptic neurons. Although no one agrees on which process is most critical for enhanced communication at the synapse, some have suggested that changes in the shape of postsynaptic cells—particularly in the spiny protrusions on dendrites—are important.

The new information gives what Bliss terms "a molecular basis" to an induction rule for LTP proposed in 1949 by Donald Hebb of McGill University in Montreal: a synapse will become stronger if the presynaptic neuron is firing at a time when the postsynaptic cell is also active. But neuroscientists are still debating about a second issue, namely, which mechanisms are required to maintain the increased synaptic communication.

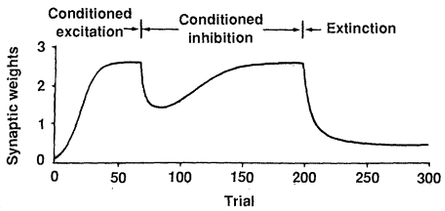
Bliss and his colleagues are looking into the issue by exploring two questions: first, whether increased neurotransmitter release can be correlated with LTP, and second, what events trigger the increased release. In their experiments with intact animals, the London researchers find that increased glutamate release is associated with LTP. Perforant path fibers, which make up an excitatory neuronal pathway leading into the hippocampal region, release more neurotransmitter for a sustained period of time after LTP has been induced.

A second critical question remains, however. How do the postsynaptic cells communicate a change to the presynaptic cells, given that the normal flow of information is in the reverse direction? "There has to be a retrograde message," says Bliss. "The presynaptic cell has to be told by the postsynaptic cell to increase its level of neurotransmitter release." As yet, the nature of this message is unknown.

Whether neuroscientists can demonstrate that these changes in the hippocampus, measured at the cellular and molecular levels, really underlie learning is an important next phase of investigation.

Model Neuron Predicts Animal Behavior

A new theoretical model of changes in neuronal activity during learning predicts many of the conditioned behaviors Pavlov described during the early 1900s. The new model is somewhat controversial because it indicates that a single nerve cell, rather than a complex network of neurons, can encode a wide range of the behaviors exhibited by an animal as it learns. "When I began this work 23 years ago, I never expected to find that a single neuron model would predict so many



A theoretical neuron model for learning *predicts conditioned behaviors described by Pavlov: conditioned excitation, conditioned inhibition, and extinction.* [*Courtesy of Harry Klopf*]

classical conditioning phenomena observed at the level of the whole animal," says Harry Klopf of Air Force Wright Aeronautical Laboratories at Wright-Patterson Air Force Base in Ohio.

In addition to having its roots in Pavlov's and more recent experimental data, Klopf's model also stems from a theoretical approach to learning described by Donald Hebb in 1949. The Hebbian model of learning, like the Pavlovian view, describes how a neuron (or animal) learns to associate one stimulus with another. But in Klopf's model, which is an extension of that proposed by Andrew Barto and Richard Sutton of the University of Massachusetts at Amherst, a neuron learns to associate a *change* in the signal it receives from another nerve cell with a change in its own frequency of firing. This modification of Hebb's postulate—that neurons associate changes in stimuli rather than the stimuli themselves—greatly improves the ability of the new model to predict conditioned behaviors.

For example, the model neuron, described by Klopf and James Morgan, also of the Wright Aeronautical Labs, can learn to perform many behaviors by computer-based training. Three of these—all of which parallel Pavlov's experiments—are conditioned excitation, conditioned inhibition, and extinction.

To generate the first behavior, Pavlov rang a bell (conditioned stimulus 1, or CS1) and then gave a dog food (unconditioned stimulus, or US). Initially, the dog salivated only in response to the strong food stimulus, but after a series of bell-food or CS1-US presentations, it learned to salivate when the bell rang. Klopf's neuron model undergoes the same form of conditioned excitation.

Klopf measures learning in terms of how strong the synapse between a presynaptic cell and the postsynaptic neuron becomes during the training procedure. The mathematical model, which relates changes in the firing frequencies of the neurons with changes in the synaptic strength, predicts an S-shaped learning curve.

The model assumes that before training begins, the synapse is working and therefore has a weight value. It predicts that when the frequency of firing increases in both the presynaptic and postsynaptic neurons because of the presentation of the conditioned and unconditioned stimuli, respectively, the synaptic weight increases. Learning, symbolized by changes in synaptic weight, levels off when the effect of the firing frequency of the presynaptic cell becomes similar in strength to the postsynaptic response.

"In a second stage of training Pavlov would ring the bell, then give the dog food," says Klopf. "A while later he would ring the bell and sound a tone as a second conditioned stimulus simultaneously with the bell, but give no food." Three things happened, in terms of the animal's behavior, and the model neuron predicts all of them.

First, one of the synaptic weights, which represents the dog's conditioned salivation response to CS1 (bell), decreases after a number of trials and then returns to its highest level. Second, the response to the presentation of CS1 (bell) and CS2 (tone) together decreases to zero, an interaction that involves a different synapse with an inhibitory effect on the postsynaptic neuron. Finally, CS2 (tone) acquires inhibitory properties and, in Pavlov's terms, becomes a "conditioned inhibitor."

In still a third phase of training, Pavlov would eliminate the food completely but continue to present the bell alone, or alternated with the bell and tone together. For this experimental paradigm, the model neuron predicts that the conditioned response associated with CS1 (bell) will extinguish or decrease to zero, whereas the conditioned inhibition associated with CS2 (tone) will not extinguish. These theoretical results indicate that the neuronal model is learning to use conditioned stimuli to anticipate unconditioned stimuli, he says.

Klopf's model differs from others not only because it predicts that a single neuron may be capable of many complex behaviors, but also because it is based on a sequential presentation of the CS and the US. This is similar to Pavlov's paradigm, but unlike the nearly simultaneous presentation of the two stimuli modeled by Hebb and used by some modern experimental neuroscientists who study learning in biological models, including the hippocampal slice (see previous briefing).

Klopf emphasizes that many different species of animals learn when researchers separate the conditioned and unconditioned stimuli with a short time delay. Models that depend on simultaneous stimuli have not yet been shown to have a clear relation to learning, he says. ■

DEBORAH M. BARNES