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Simple Chemical Switches Steer Migrating Neurons

In an embryo's developing brain and spinal cord, the growing ends of nerve cells, called axons, travel great distances to make precise connections with other neurons. Without such accurate connectivity, the nervous system would never wire properly.

An axon's path towards a target neuron is steered by growth cones that are located in the tip of the axon. These growth cones receive cues about the best path to follow from chemical attractants and repellents secreted by cells in the central nervous system.

Until recently, scientists assumed that type of neuron and the unique chemical receptors found on its surface determined whether a neuron is attracted to or repelled by a given guidance chemical. Now, HHMI investigator Marc Tessier-Lavigne at the University of California, San Francisco, working with Mu-ming Poo and colleagues at the University of California, San Diego (UCSD), has found that a single chemical cue can either attract or repel, depending on the growth cone's internal status. This research is reported in the September 4, 1998, issue of the journal *Science*.

This work, says Tessier-Lavigne, may hold promise for regenerating nerves damaged by spinal cord injury. It also provides potentially important clues for understanding disorders of neuronal migration, which may be responsible for childhood epilepsy, forms of mental retardation, and possibly dyslexia and schizophrenia.

The researchers found that two key signaling chemicals, cyclic AMP and cyclic GMP, located in the growth cone, act as switches. In general, increasing levels of these cyclic nucleotides promotes attraction, while lowering levels favors repulsion. Thus, both attraction and repulsion share a common chemical switch.

In studying spinal cord neurons cultured from frog embryos, the investigators found evidence of two steering-related circuits within the growth cones, one responding to cyclic AMP, the other to cyclic GMP. For example, a repulsive signal—where growth cones turn away from the source of the chemical cue—became attractive when cyclic GMP was added to the growing neurons.

In contrast, a different repulsive signal became attractive when cyclic AMP was added to the growing neurons.

Several years ago, Tessier-Lavigne's group discovered netrin-1, a chemical that attracts growth cones. In an article published in *Neuron* in December 1997, Tessier-Lavigne's and Poo's groups showed that netrin-1 can also repel growth cones when cyclic AMP is lowered. Both the attraction and the repulsion were abolished by lowering calcium levels. In the article published in *Science*, the researchers show that calcium dependence emerged as a consistent feature of cues influenced by the cyclic AMP circuit.

"It's remarkable that all five cues we've looked at so far fit this simple picture," said Tessier-Lavigne. "We seem to be tapping into some primordial guidance mechanisms. The growth cone is a machine designed to respond to the environment by turning one way or the other, so maybe it's not so surprising there are only a limited number of ways of accessing that machine."

That is not the end of the story, however. Cyclic AMP and cyclic GMP levels are controlled by other factors in the growth cone's ever-changing external environment. This, says Tessier-Lavigne, suggests that "the response of a growth cone to a particular guidance cue may depend critically on other signals received by the neuron. The susceptibility to conversion between attraction and repulsion may enable a growing axon to respond differentially to the same guidance cue at different points along the journey to its final target."

In an accompanying commentary in the same issue of *Science*, Pico Caroni of the Miescher Institute in Switzerland cites as "most exciting" the possibility that damaged nerves might be regenerated by treating them with drugs that boost the levels of these molecular cues, reversing the action of repulsive factors.

For example, MAG, a component of a neuron's protective myelin sheath, is known to actively block axonal regeneration. The researchers showed that MAG, which is normally repellent, can become an attractant when cyclic AMP levels are raised.

"Since many different inhibitory factors that prevent regeneration likely act through these chemical cue systems, we have a better chance of reversing all inhibitory actions by this type of manipulation," said Poo. He also noted that experiments in live animals would follow, and—assuming those studies are promising—eventually clinical trials in humans.

In vivo studies will be needed to test whether the switching mechanism discovered in the cell culture model is actually being used by the developing organism, added Tessier-Lavigne.