Genes for learning, remembering, forgetting: Proteins important in embryos found to change the adult brain

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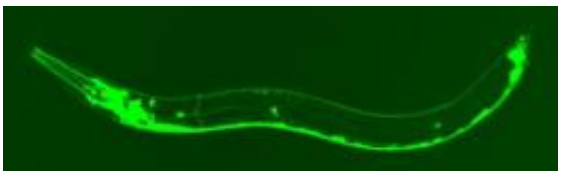

This is a microscope image of the roundworm or nematode *C. elegans* with its nervous system glowing green due to labeling with a green jellyfish protein. Credit: Penelope Brockie, University of Utah.

Certain genes and proteins that promote growth and development of embryos also play a surprising role in sending chemical signals that help adults learn, remember, forget and perhaps become addicted, University of Utah biologists have discovered.

"We found that these molecules and signaling pathways [named Wnt] do not retire after development of the organism, but have a new and surprising role in the adult. They are called back to action to change the properties of the nervous system in response to experience," says biology Professor Andres Villu Maricq, senior author of the new study in the March 30 issue of the journal *Cell*.

The study was performed in C. elegans – the millimeter-long roundworm

or nematode – which has a nervous system that serves as a model for those of vertebrate animals, including humans.

Because other Wnt pathways in worms are known to work in humans too, the researchers believe that Wnt genes, the Wnt proteins they produce and so-called "Wnt signaling" also are involved in human learning, memory and forgetting.

"Almost certainly what we have discovered is going on in our brain as well," Maricq says. And because a worm nerve-signal "receptor" in the study is analogous to a human nicotine receptor involved in addiction, schizophrenia and some other mental disorders, some of the genes identified in the worm study "represent possible new targets for treatment of schizophrenia and perhaps addiction," he adds.

Wnt genes and their proteins already were known to "pattern the development and distribution of organs in the body" during embryo development, and to be responsible for various cancers and developmental defects when mutated, he says.

Maricq conducted the study with these Utah biologists: doctoral students Michael Jensen and Dane Maxfield; postdoctoral researchers Michael M. Francis, Frederic Hoerndli and Rui Wang; undergraduate Erica Johnson; Penelope Brockie, a research associate professor; and David M. Madsen, a senior research specialist. The study was funded by the National Institutes of Health and the American Heart Association.

Synapse Plasticity is the Basis of Learning and Memory

Synapses are the connections between nerve cells (neurons). Nerve signals are transmitted through synapses. Learning and memory concern

how these connections are made, broken, strengthened or weakened. Proteins known as receptors are delivered to the synapses or removed from them to strengthen or weaken the connection.

In the new study, Maricq and colleagues identified a "Wnt signaling pathway" – a series of genes and the proteins they produce – that controls the strength of nerve signal transmission from one neuron through a synapse to the next neuron. This allows "plasticity" of synapses – a key factor in learning, retaining memories and forgetting.

"The adult nervous system is not a stagnant tissue, but rather dynamic and plastic, with the strength of synapses – specialized neuron-to-neuron connections – changing with experience, learning and memory," Maricq says. "It's not a fixed thing, like when you're done making the heart, you're done."

When synapses and thus incoming nerve signals are strengthened by adding receptors, an organism learns and remembers; when the opposite occurs, the organism forgets, he adds.

How is that connection strengthened or weakened? When one neuron sends a nerve signal to another neuron, the first neuron releases a chemical known as a neurotransmitter, which moves through the synapse connecting the two cells and attaches or binds to receptors on the surface of the second neuron.

"You can think of the receptors like amplifiers, like hearing aids," Maricq says.

The volume of the received nerve signal depends on the number of receptors, which are stored in a supply depot just below the nerve cell's surface.

The Wnt signaling identified in the new study "tells the depot to put more receptors into the synapse – or not," says Maricq.

He emphasizes that the Wnt chemical signal is different than the actual nerve signal carried by a neurotransmitter chemical, which in the new study was acetylcholine. The Wnt signal "is a secondary signal that controls the volume of the neurotransmitter signal," Maricq says.

Worms Reveal Details of Nerve Signal Volume Control

By crippling various genes in the worms, the researchers identified the "signaling pathway" by which a Wnt protein in one nerve cell sends a chemical signal to another cell telling it to increase the number of receptors on its surface, thus increasing the strength or volume of nerve signals between the cells.

The type of nerve-signal receptor in the study is an acetylcholine receptor named ACR-16. When researchers crippled the gene that makes the ACR-16 receptor protein, there were not enough receptors, so nerve signals were disrupted and the worms "had uncoordinated movement," Maricq says. "They were semi-paralyzed."

The scientists found mutations of other genes that also resulted in inadequate ACR-16 receptors and impaired the worms' movement. They discovered such genes belong to the "Wnt signaling pathway" that puts enough receptors on the cell surface so signals can be received.

Besides ACR-16, genes in that pathway produced proteins named CWN-2 – which is a Wnt protein – LIN-17, CAM-1 and DSH-1.

Here is how that pathway controls the volume of incoming nerve signals:

1. A neuron releases CWN-2, which binds onto a receptor protein on the signal-receiving cell. That protein is a newly discovered combination of the LIN-17 and CAM-1 proteins.
2. The LIN-17/CAM-1 protein sends a signal to a protein called disheveled, or DSH-1.
3. "DSH-1 somehow sends the volume-control signal" that dispatches more ACR-16 receptors from depots inside the second neuron to that cell's surface, thus boosting the volume of the received nerve signal, Maricq says.

The researchers used a green jellyfish protein to mark the ACR-16 receptors so they were visible under a microscope. When any of the genes in the Wnt signaling pathway were mutant, the scientists could see the green-labeled receptors accumulate under the surfaces of nerve cells instead of moving to the surface.

Another experiment recorded electrical currents in worm nerve synapses and found it was smaller when any of the Wnt pathway genes were mutated. The smaller current – reflecting impaired nerve-signal transmission – explains why the mutant worms were partially paralyzed.

Human Version of Worm Receptor Tied to Mental Disorders

The ACR-16 acetylcholine receptor is the worm version of the alpha-7 nicotinic acetylcholine receptor in humans and other vertebrates. Both are similar in structure and function in animals from worms to fruit flies, mice and people.

The alpha-7 receptor "is important in schizophrenia and a number of

different mental disorders, and may have a role in addiction, but we don't understand how it's regulated," Maricq says.

Many existing psychiatric drugs modify synapse strength. The new study suggests research should be done to show if the same Wnt signaling genes in worms also control alpha-7 receptor levels on human brain cells. If so, new drugs might be developed to target those genes as a way to treat mental disorders, including addiction.

"Addiction is like learning at a primitive level," Maricq says. "Addiction means that somewhere in your brain, synapses are too strong. So you want more."

Provided by University of Utah