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## Relax and Learn: New Drugs that Help DNA Unwind May Improve Memory

New research suggests that brain cells prepare to store new memories by first unwinding a little. Howard Hughes Medical Institute scientists have identified a protein that hampers learning and memory by keeping DNA inside neurons tightly coiled and unable to “relax,” according to a new study published in the May 7, 2009, issue of *Nature*.

Compounds that block the activity of this newly identified protein appear to enhance memory in mice. The drugs boost memory by permitting DNA inside neurons to relax, thereby giving enzymes access to genes that must be turned on to enable learning. Some of those drugs are already being evaluated as potential anti-cancer therapies. They may also help treat memory loss associated with Alzheimer’s disease and other neurodegenerative diseases, said HHMI investigator Li-Huei Tsai at the Massachusetts Institute of Technology.

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When people learn, connections between their brain cells—synapses—reshuffle and strengthen. Some ephemeral learning takes place within seconds or minutes of, say, looking up a phone number or navigating a new route to the store. That information is stored for a short time and usually disappears soon after the task is completed. To make memories stick, a certain cadre of genes must be activated in the brain. And to activate the genes needed for learning and memory, the DNA inside neurons and the protein spools around which it is wrapped -- the histones -- must unwind.

Histones are covered with chemical tags called acetyl groups, which mark specific segments of DNA that need to be relaxed so enzymes can gain access and turn those genes on. Previous studies suggested that adding or removing

acetyl groups influences learning and memory by encouraging the growth of neurons. For instance, Tsai had previously shown that inhibiting histone deacetylase (HDAC) proteins, the enzymes that remove acetyl groups, improved memory in mice with gene mutations that cause a disease similar to Alzheimer's disease. "All you need to do is increase histone acetylation and you can rescue the memory deficits," says Tsai.

Tsai began to wonder whether inhibiting such enzymes could help slow memory loss in patients with neurodegenerative disorders. Her earlier studies were done with general HDAC inhibitors, which do not discriminate between the 11 subtly different HDAC proteins in the cells of humans and mice. To reduce the risk of side effects, Tsai wanted to target only those HDAC proteins relevant to learning and memory. But she first needed to design experiments to find them. "If you want to have a more selective drug, you need to have some idea of which of the 11 HDACs are involved in learning and memory," she says.

To home in on the particular HDACs involved, Tsai and her colleagues tested several different drugs that inhibit HDAC activity in mice. They found that only those compounds that targeted HDAC1 or HDAC2 improved memory in the mice. Earlier studies by a group of researchers led by HHMI investigator Eric Kandel showed that one of those drugs, SAHA, improved memory in a mouse model of Rubinstein-Taybi syndrome, a condition characterized by short stature and moderate to severe learning difficulties.

To dig deeper, they studied lines of mice that produced unusually large amounts of HDAC1 or HDAC2. Using several memory tests, they found that mice with extra HDAC1 learned just as well as normal animals, but mice with boosted HDAC2 were slow learners. That suggested that HDAC2, but not HDAC1, was responsible for impaired learning. Further studies confirmed that animals lacking HDAC2 performed better than normal in the memory tests.

The researchers then examined the brain tissue of animals with and without the HDAC2 protein. Neurons lacking HDAC2 formed a greater than normal number of synapses with neighboring cells, whereas cells with a greater quantity of HDAC2 made few synapses. Moreover, genes involved in learning and memory were more active in mice without HDAC2; those genes were quieter in animals with extra HDAC2.

Tsai's team also found that SAHA enhanced learning in animals with boosted HDAC2. But SAHA had no effect on learning in animals that did not have HDAC2, suggesting that SAHA improves memory by blocking HDAC2. "This is a mechanism that can serve as a master switch that can coordinately regulate a whole set of genes involved in learning and memory," says Tsai.

Tsai acknowledges that testing HDAC2-blockers on humans is not likely to happen anytime soon. "Now that we've identified a major target, the next question is whether we or someone else can come up with very selective small molecules," says Tsai. If researchers can zero in on this kind of molecule, she is optimistic that they'll help people with a variety of

learning-related problems. “I suspect they’ll be beneficial in Alzheimer’s disease, other types of dementia, and mental retardation,” she says.

She also wants to investigate whether drugs that encourage DNA to relax could help other conditions. For instance, Tsai wants to test HDAC2 blockers in mouse models of autism. The social and communication problems typical of autism seem to result from faulty wiring in the brain, and making learning easier could help the brain rewire correctly. Encouraging acetylation could even help schizophrenia, which also results from wiring problems. Although cancer researchers have explored HDAC inhibitors for many years, Tsai says they are new to the field of neuroscience. “People are very excited,” she says. Unraveling the puzzle of how unwinding DNA helps learning and memory could mean new hope for people with a variety of learning disorders.