

Retrieving Lost Memories

Scientists have found that certain substances, at least in the lab, prevent neurodegeneration from Alzheimer’s disease and restore what was seemingly forgotten.

LI-HUEI TSAI RECALLS A LIFE-SHAPING EVENT WHEN SHE WAS A TODDLER living with her grandmother in Taiwan. “Every morning we took a short walk to the local market for groceries. One day, on the way back, there was a thunderstorm, so we took shelter in a little shed. After the rain, I said, ‘Let’s go home now.’ I looked at my grandmother’s face and it was completely without expression. ‘Home?’ she asked. ‘Where is home?’”

Mystified and frightened at the time, Tsai came to understand that her grandmother, then in her 50s, probably had early-onset Alzheimer’s disease, a heritable form of the mind-robbing illness that strikes victims in the prime of life. Now an HHMI investigator at the Massachusetts Institute of Technology (MIT), Tsai’s mission is to end Alzheimer’s disease. “That memory and others like it,” she says, “are a big source of my inspiration to carry out this line of research.”

Four years ago, her research team created a powerful mouse model that, unlike most previous models, shows the hallmarks of human Alzheimer’s disease: massive loss of neurons, the presence of neurofibrillary tangles, and accumulation of amyloid peptides in the brain, accompanied by severe memory loss. What’s more, the extensive and rapid brain deterioration in the mice can be quickly turned on and off. “These two characteristics render the mice ideal for looking for potential therapeutics,” Tsai says.

Her recent studies focus on a class of enzymes called histone deacetylases (HDACs), which perform many functions in cells and derive their name from their ability to remove small chemical tags, called acetyl groups, from histone proteins—key components of chromosomes. Because histone acetylation patterns can influence gene expression, HDACs have widespread physiological consequences, including in Alzheimer’s disease, as Tsai’s team first reported in the online version of *Nature* last April. They were investigating a well-described but poorly understood phenomenon called “fluctuating memory,” in which even advanced-stage Alzheimer’s patients suddenly regain, at least for a short while,

seemingly long-gone remembrances. Caretakers have noted that immersing Alzheimer’s patients in intellectually stimulating environments tends to evoke these lucid moments.

Remarkably, Tsai and her colleagues observed the same phenomenon in the lab. After inducing Alzheimer’s disease in mice that had been taught a battery of learning and memory tasks, they found that those housed in cages with toys and other intellectual stimulation regained “lost” memories of their acquired skills, but the lessons learned by those kept in spartan cages remained forgotten.

When they examined the acetylation patterns of brain histones in these two groups of mice, researchers discovered that the patterns differed dramatically. With that finding, complemented by prior reports of the beneficial effect of HDAC inhibitors on learning and

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memory, the Tsai team was motivated to test such agents on its mouse model. They discovered that administering an HDAC inhibitor—sodium butyrate or trichostatin A—to the mice instead of environmental enrichment was enough to restore lost memories.

“The brains of the treated mice didn’t look any bigger and the number of cells in the brain didn’t look significantly different from those of untreated mice,” says Tsai. “But it seemed that the existing neurons were more active in communicating with each other and making more synapses.”

Tsai cites recent studies on an HDAC called SIR2, which shows anti-aging properties in many organisms. “Alzheimer’s disease is a typical product of aging,” she says. “So to me, it’s quite logical that the next question was whether SIR2 might also be beneficial in treating this illness.” With her colleague David Sinclair’s research team at Harvard Medical School, Tsai’s group tested that notion using the MIT mice and then reported their findings last June in the online version of *The EMBO Journal*. The overexpression of SIRT1—the human version of SIR2—in the mice not only protected them from

neurodegeneration but preserved their cognitive and memory functions as well.

The scientists also tested the neuroprotective effects of resveratrol, the compound in red wine that has attracted considerable scientific and media attention for its possible anti-aging properties. They found that resveratrol, an activator of SIRT1, offered the mice substantial protection from neurodegeneration and preserved their learning ability. Just how SIRT1 protects the brain is unclear to

Tsai, since the enzyme targets many other protein substrates besides histones, but her team is trying to pin down its biochemical role in the brain.

Given these experimental results, Tsai is “cautiously optimistic” that new drugs for preventing, even reversing, the effects of Alzheimer’s disease may become realities in the not-too-distant future. “I can’t tell you it’s a year or two from now,” she says, “but I don’t think it will be as long as 10 years.” ■ —PAUL MUHLRAD



Results from studies in the lab of Li-Huei Tsai suggest that “memory loss” may be an inaccurate description of certain mental deficits associated with neurodegenerative diseases.