

One shot of a kidney protein gave monkeys a brain boost

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Klotho, the ancient Greek goddess of fate, is responsible for spinning the thread of life. In the human body, a protein with the same name might also be able to bring some life back to an aging brain.

In a study published today in the journal *Nature Aging*, researchers at Yale and the University of California, San Francisco found that a single injection of the klotho protein led to modest improvements in cognitive function in older monkeys and that the effects lasted for two weeks. The authors think the protein represents a promising avenue for researching the rejuvenation of brain function in older adults.

“Cognitive decline from aging is one of our most pressing biomedical problems without truly effective medicines,” says Dena Dubal, a professor of neurology at UCSF and the study’s senior author. After discovering—accidentally—in previous work that klotho boosts cognition in mice, she says, “it became important to test this in a brain like ours.”

Produced by the kidney, klotho circulates in the blood and has been linked to health and lifespan. Orson Moe, a kidney specialist and professor of internal medicine at the

University of Texas Southwestern Medical Center, describes it as a housekeeper that helps regulate the kidneys and metabolism. "It protects us and keeps us healthy," he says.

The protein was first discovered in 1997 by pathologist Makoto Kuro-o at the National Institute of Neuroscience in Tokyo. He demonstrated that mice lacking klotho suffered from what he called a "syndrome that resembles human aging." They had early onset heart disease, cancer, cognitive decline, and organ failure. Kuro-o later found that mice that made more klotho lived 20 to 30 percent longer than those with normal levels.

In people, having more of the protein seems to carry health benefits. Although klotho levels naturally decrease with age, some people have more of it than others. In a 2014 paper, Dubal and her colleagues studied more than 700 participants ages 52 to 85. Those with higher levels of the protein—about one in five people studied—performed better on thinking and memory tests, such as drawing a recalled image and naming the color of a word shown in a different color.

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For that study with mice, the team also engineered mice to have higher than normal levels of the protein—these mice performed better on maze tests than normal mice.

In the current study, Dubal and her coauthors wanted to see if klotho would have the same effects on monkeys, which are often used as a stand-in for humans because of their genetic similarities. As people get older, their working memory—the ability to hold something in mind, like a phone number—worsens. Dubal's research team tested the working memory capacity of 18 rhesus macaques, whose ages were about equivalent to 65 in human years. Each had to remember the location of a hidden treat in an array of compartments—a common lab test the researchers chose because it relies on working memory and doesn't get easier over time.

They then administered a single low dose of klotho under each monkey's skin, raising levels of the protein to those normally present in the animals at birth. Four hours later, researchers had them complete the food-finding task in batches of 20 trials, and the team then retested the monkeys over the next two weeks. Overall, the animals made correct choices more often than they did before receiving the injection. The team tested monkeys on two versions of the task: an easier one, where there were fewer compartments to choose from, and a harder one with more of them. Klotho improved their performance on the easier task by about 6 percent, and on the harder version by about 20 percent, Dubal says.

"This is very encouraging," says Moe, who wasn't involved in the new study.

The researchers had the monkeys do the task several times over the course of two weeks, and the team saw that even though klotho gets broken down by the body within a couple days of injection, the cognitive-enhancing effect lasted the entire time. "The fact that it can be given once and last for two weeks seems great, although we don't know at this point whether repeated administration would work again," says Eric Verdin, CEO of the Buck Institute for Research on Aging, who wasn't involved in the study.

In fact, in previous studies with mice, both low and high doses of klotho boosted cognition, helping them perform better in several maze tasks that challenge learning and memory. But when Dubal's team gave monkeys doses of 10, 20, and 30 micrograms per kilogram of body weight, the benefits plateaued at the 10-microgram dose. This raises an important flag for researchers, as they consider someday testing klotho injections in humans. When it comes to dosing, Verdin says, "More is not always better."

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