Hormone shows promise as cognition enhancer

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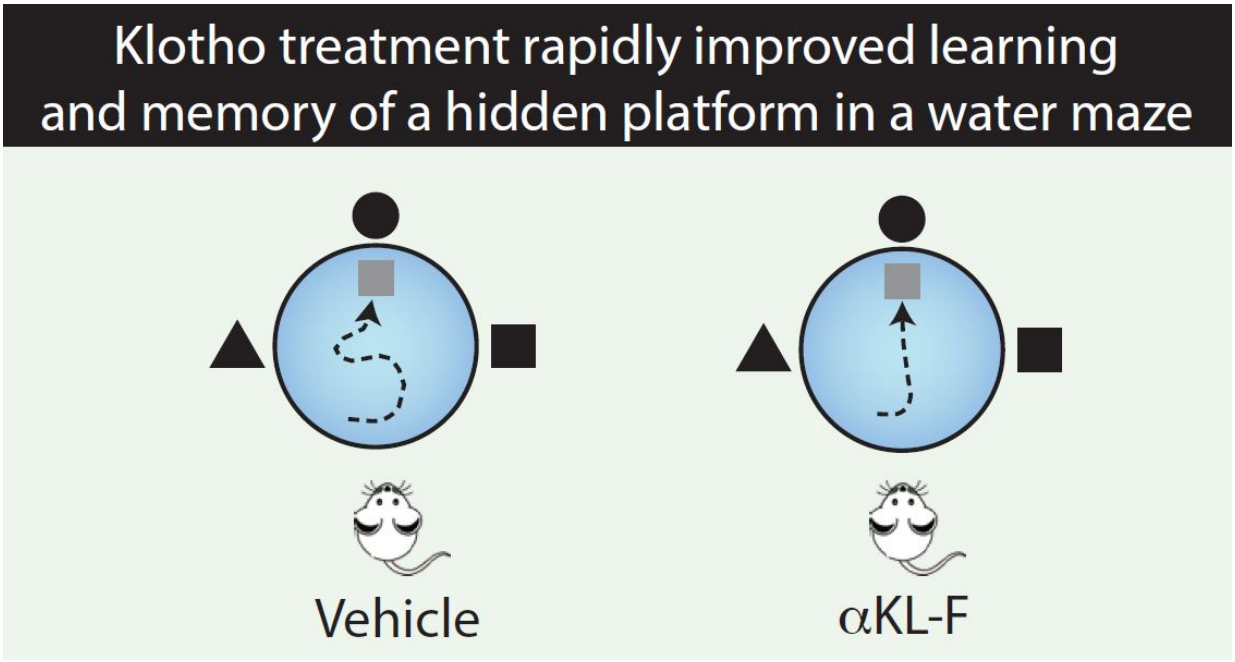

This illustration shows how klotho treatment in mice rapidly improved learning and memory of a hidden platform in a water maze. Credit: Leon et al.

In a study that augurs well for the therapeutic potential of klotho - a life-extending protein hormone that a minority of people naturally produce at high levels - scientists at UC San Francisco have found that administering a fragment of the klotho protein to young, aging or impaired mice rapidly improves their cognitive and physical

performance.

While previous studies had revealed associations between elevated klotho levels and better cognition, that research had been done with mice genetically engineered to continuously produce high klotho levels and in people carrying genetic variants that caused them to have high klotho levels throughout life. As a result, it was still unclear whether klotho could be administered like a drug to rapidly enhance cognitive functioning in mice or people with normal or low levels of the hormone.

"The burning question in the field was, 'Does klotho have therapeutic potential?'" said Dena Dubal, MD, PhD, associate professor of neurology, David A. Coulter Endowed Chair in Aging and Neurodegenerative Disease at UCSF, and senior author of the new paper. "We now know that, yes, it does."

The study, published online Aug. 8, 2017, in *Cell Reports*, showed clear evidence of improved cognition across a range of domains - including spatial learning and memory, as well as working memory. But it remains unexplained how the piece of the klotho hormone that the researchers injected into the bodies of the mice caused these effects, since there is no evidence that klotho is able to enter the brain from the bloodstream.

"It makes us wonder about the connection between the body and the brain," said Dubal, a member of the UCSF Weill Institute for Neurosciences. "What we saw with acute klotho administration may be similar to what happens with exercise, which also improves cognition and brain health, although we don't know how."

The beneficial effects that Dubal and her team saw in young mice occurred within hours, and they far outlasted the time that klotho remained active in the body. "It suggests to me that there is a long-lasting effect of even a single treatment, and it probably has to do with the

remodeling of synapses, the sites where communication among nerve cells takes place," she said.

The team also tested aged mice that, at 18 months old, are at about the same stage in the mouse lifespan as a 65-year-old human, and found that a single injection of klotho was enough to significantly improve their ability to navigate and to learn new tasks.

The researchers then looked at mice that were engineered to produce a human protein called alpha-synuclein, which is a hallmark of Parkinson's disease and contributes to Alzheimer's disease. Alpha-synuclein is believed to contribute to the movement disturbances seen in Parkinson's. Giving klotho to these mice improved their motor function. The klotho-treated mice also learned better and were more willing than untreated mice to explore new territory, even though their brains remained loaded with toxic proteins. This suggests that the treatment might somehow make diseased brains more resilient.

"There's stronger and stronger evidence that the body works in a very integrated way, and that systemic effects profoundly affect the resilience of our brain," Dubal said.

Klotho, which is naturally produced in both the kidney and the brain, is a complex hormone that affects many different systems in the body, and it has several forms. Once produced, it lodges itself in cell membranes, then enzymes cleave off a portion that circulates in the blood and the cerebrospinal fluid that bathes the brain and spinal cord.

The klotho fragment that Dubal's team injected into mice is similar to the cleaved piece of the hormone that naturally circulates in the blood. But since klotho does not cross the so-called blood-brain barrier, which blocks the entry of some substances from the general circulation into the brain, researchers do not know exactly how it alters brain function.

Members of Dubal's lab had previously shown that mice carrying genetic modifications that exposed them to high klotho levels from birth had greater numbers of a synaptic protein called the GluN2B subunit, which is implicated in long-term potentiation, a strengthening of synapses that is critical to learning and memory. The researchers leading the current study expected to find a greater abundance of GluN2B in the klotho-treated mice, but they did not.

Instead, "after many months of repeating experiments and analyzing the data, we slowly realized that klotho treatment was increasing activation of the subunits that were already there," said Julio Leon, PhD, first author and a postdoctoral fellow in Dubal's lab.

To confirm these findings, the researchers selectively blocked the GluN2B subunits to see if they could still be activated by klotho, and found that they could not. Then they performed an unbiased analysis of about 4,000 proteins to see which ones changed together in the brains of the klotho-treated mice, an analysis that pointed to glutamate receptor signaling, which involves GluN2B, as the main pathway affected by klotho treatment.

Dubal said the new findings, along with others like the experiments involving exercise or those in which older mice have been rejuvenated with blood from younger mice, are helping to illuminate the dimly understood connections between the body and the brain.

"All of this work is going to teach us something really important about how the body transmits resilience to the brain," she said. "That's where this is taking us."

More information: *Cell Reports*, Leon et al.: "Peripheral Elevation of a Klotho Fragment Enhances Brain Function and Resilience in Young, Aging, and α-Synuclein Transgenic Mice" www.cell.com/cell-

reports/full … 2211-1247(17)30990-7 , DOI: 10.1016/j.celrep.2017.07.024