A drug that extends life span prevents Alzheimer's deficits

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If research results continue to be repeated and are turned into clinical trials, a drug already approved for some uses could be marshaled -- sooner than we expect -- to prevent Alzheimer's disease in humans and improve health to the end of life.

A few weeks after a report that rapamycin, a drug that extends lifespan in mice and that is currently used in transplant patients, curbed the effects of Alzheimer's disease in mice, a second group is announcing similar results in an entirely different mouse model of early Alzheimer's.

Both reports are from The University of Texas Health Science Center at San Antonio, where the rapamycin studies are conducted in the Sam and Ann Barshop Institute for Longevity and Aging Studies and in basic science departments.

The second report, released April 1 by the journal PLoS ONE, published by the Public Library of Science, , showed that administration of rapamycin improved learning and memory in a strain of mice engineered to develop Alzheimer's. The improvements in learning and memory were detected in a water maze activity test that is designed to measure learning and spatial memory. The improvements in learning and memory correlated with lower damage in brain tissue.

Less sticky

"Rapamycin treatment lowered levels of amyloid-beta-42, a major toxic species of molecules in Alzheimer's disease," said Veronica Galvan, Ph.D., assistant professor from the Barshop Institute and the Department of Physiology. "These molecules, which stick to each other, are suspected to play a key role in the early memory failure of Alzheimer's."

This strain of mice has been engineered to have defects in the genes that make amyloid precursor protein, ultimately resulting in the abnormal accumulation of amyloid-beta-42 that dampens synaptic connections. Synapses are junctions where neurons communicate with each other, providing the essential "wiring" for normal function of the brain. Without this communication, neurons die, leading to the memory losses seen in Alzheimer's.

Longer life for mice

In July 2009, Barshop Institute researchers and colleagues at two other institutions reported that microencapsulated rapamycin extended the life span of mice, possibly by delaying aging. A bacterial product first isolated from soil of Easter Island, rapamycin is approved by the U.S. Food & Drug Administration to prevent organ rejection in transplant patients. Rapamycin is the first pharmacologic intervention shown to extend life in an animal model of aging.

If rapamycin treatment indeed delays aging in mice, are age-associated diseases, such as Alzheimer's, delayed or blocked? The new study, authored by Spilman et al, sought to answer this question. In the study, the same rapamycin-supplemented diet as in the life span study was fed to groups of the Alzheimer's-susceptible mice and their normal littermates. A non-rapamycin diet was fed to control groups. Rapamycin feeding began at 4 months of age, when the susceptible mice show high amyloid-beta-42 levels and synaptic dysfunction, but do not yet have amyloid beta plaques or spatial memory impairments.

Get out of the water

After 13 weeks of treatment, all groups were trained in the water maze exercise to see how quickly they could learn to exit the water via a hidden platform. Doing so requires the use of spatial cues, such as patterned posters or photos, positioned all around the water tank. The Alzheimer's model mice that were fed the control diet predictably showed significant losses in learning and memory and reduced performance.

"Strikingly, the Alzheimer's mice treated with rapamycin displayed improved performance on the maze, even reaching levels that were indistinguishable from their normal littermates," Dr. Galvan said. "Levels of amyloid-beta-42 were also reduced in these mice after treatment, and we are seeing preserved numbers of synaptic elements in the brain areas of Alzheimer's disease mice that are ravaged by the disease process."

Intriguingly, differences in resistance to swimming in the middle of the pool (a measure of anxiety) and in floating (a measure of hopelessness) were not observed among groups. "This suggests that improved performance in rapamycin-treated, Alzheimer's-susceptible mice is a result of effects on purely cognitive processes but is not due to effects related to non-cognitive components of behavior, such as helplessness and anxiety," Dr. Galvan said.

Changing a toxic process

"The fact that we are seeing identical results in two vastly different mouse models of Alzheimer's disease," Dr. Galvan added, in reference to the recent study by Caccamo et al, "provides robust evidence that rapamycin treatment is effective and is acting by changing a basic

pathogenic process of Alzheimer's that is common to both mouse models. This suggests that it may be an effective treatment for Alzheimer's in humans, who also have very diverse genetic makeup and life histories."

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