Chronic Stress Spawns Protein Aggregates Linked to AD

Scott LaFee, UCSD Health Sciences News

Repeated stress triggers the production and accumulation of insoluble tau protein aggregates inside the brain cells of mice, say researchers at the University of California, San Diego School of Medicine in a new study published in the March 26 Online Early Edition of the Proceedings of the National Academy of Sciences.

The aggregates are similar to neurofibrillary tangles or NFTs, modified protein structures that are one of the physiological hallmarks of Alzheimer’s disease. Lead author Robert A. Rissman, PhD, assistant professor of neurosciences, said the findings may at least partly explain why clinical studies have found a strong link between people prone to stress and development of sporadic Alzheimer’s disease (AD), which accounts for up to 95 percent of all AD cases in humans.

“In the mouse models, we found that repeated episodes of emotional stress, which has been demonstrated to be comparable to what humans might experience in ordinary life, resulted in the phosphorylation and altered solubility of tau proteins in neurons,” Rissman said. “These events are critical in the development of NFT pathology in Alzheimer’s disease.”

The effect was most notable in the hippocampus, said Rissman, a region of the brain linked to the formation, organization and storage of memories. In AD patients, the hippocampus is typically the first region of the brain affected by tau pathology and the hardest-hit, with substantial cell death and shrinkage.

Not all forms of stress are equally threatening. In earlier research, Rissman and colleagues reported that acute stress – a single, passing episode – does not result in lasting, debilitating long lasting changes in accumulation of phosphorylated tau. Acute stress-induced modifications in the cell are transient, he said, and on the whole, probably beneficial.

“Acute stress may be useful for brain plasticity and helping to facilitate learning. Chronic stress and continuous activation of stress pathways may lead to pathological changes in stress circuitry. It may be too much of a good thing.” As people age, perhaps their neuronal circuits do too, he said, becoming less robust and perhaps less capable of completely rebounding from the effects of stress.

“Age is the primary, known risk factor for Alzheimer’s disease. It may be that as we age, our neurons just aren’t as plastic as they once were and some succumb.”
The researchers observed that stress cues impacted two key corticotropin-releasing factor receptors, suggesting a target for potential therapies. Rissman noted drugs already exist and are in human trials (for other conditions) that modulate the activity of these receptors.

“You can’t eliminate stress. We all need to be able to respond at some level to stressful stimuli. The idea is to use an antagonist molecule to reduce the effects of stress upon neurons. The stress system can still respond, but the response in the brain and hippocampus would be toned down so that it doesn’t result in harmful, permanent damage.”

Co-authors of the paper are Michael A. Staup and Allyson Roe Lee, UCSD Department of Neurosciences; Nicholas J. Justice, Baylor College of Medicine; and Kenner C. Rice NIDA/NIH, Wylie Vale and Paul E. Sawchenko, The Salk Institute for Biological Studies.

*The authors dedicate this work to long time mentor and colleague, Dr. Wylie Vale, whose years of pioneering work deciphering and describing the stress system were fundamental to this paper. Vale passed away earlier this year at the age of 70.*

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**Late Breaking from the AAN…**

**More Evidence of the Cognitive Benefits of Exercise - The American Academy of Neurology**

Daily physical exercise may reduce the risk of Alzheimer's disease, even in people over the age of 80, according to a study published in the April 18, 2012, online issue of Neurology®, the medical journal of the American Academy of Neurology.

“The study showed that not only exercise but also activities such as cooking, washing the dishes and cleaning are associated with a reduced risk of Alzheimer’s disease,” said study author Aron S. Buchman, MD, with Rush University Medical Center in Chicago and a member of the American Academy of Neurology. “These results provide support for efforts to encourage physical activity in even very old people who might not be able to participate in formal exercise but can still benefit from a more active lifestyle.”

For the study, a group of 716 people with an average age of 82 wore an actigraph, a device that monitors activity, on their non-dominant wrist continuously for 10 days. All exercise and non-exercise was recorded. They also were given annual tests during the four-year study that measured memory and thinking abilities. During the study, 71 people developed Alzheimer's disease.

Participants also self-reported their physical and social activity. Buchman said this is the first study to use an objective measurement of physical activity in addition to self-reporting. “This is important because people may not be able to remember the details correctly,” he said.

The research found that people in the bottom 10 percent of daily physical activity were more than twice as likely to develop Alzheimer’s disease as people in the top 10 percent of daily activity.

The study also showed that those people in the bottom 10 percent of intensity of physical activity were almost three times as likely to develop Alzheimer’s disease as people in the top 10 percent of intensity of physical activity.

“Since the actigraph was attached to the wrist, activities like cooking, washing the dishes, playing cards and even moving a wheelchair with a person’s arms were associated with a lower Alzheimer’s risk,” said Michal Schnaider-Beeri, PhD, of Mount Sinai School of Medicine in New York in an accompanying editorial. “These are low-cost, easily accessible and side-effect free activities people can do at any age, including very old age, to possibly prevent Alzheimer's disease.”

The study was supported by the National Institute on Aging, the Illinois Department of Public Health and the Robert C. Borwell Endowment Fund.

To learn more about Alzheimer's disease, visit [http://www.aan.com/patients](http://www.aan.com/patients).

The American Academy of Neurology, an association of more than 25,000 neurologists and neuroscience professionals, is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a doctor with specialized training in diagnosing, treating and managing disorders of the brain and nervous system such as Alzheimer’s disease, stroke, migraine, multiple sclerosis, brain injury, Parkinson’s disease and epilepsy.
Alzheimer’s takes a heavy toll on women

Women are the epicenter of the Alzheimer’s disease epidemic. According to Alzheimer’s Association research, two-thirds of the people over 65 who have Alzheimer’s (3.3 million of the estimated 5.4 million) in the United States are women. Among the 11.2 million Alzheimer’s and dementia caregivers, 60 percent (6.7 million) are women.

That means 10 million American women either have Alzheimer’s or are caring for someone with the disease.

“With statistics consistently pointing to the fact that more women are living with Alzheimer’s and caring for people with Alzheimer’s, it is clear women are disproportionately affected by this disease,” said Angela Geiger, Alzheimer’s Association chief strategy officer.

Numbers don’t tell the entire story of the emotional, mental and physical toll Alzheimer’s takes on people with the disease and their caregivers. However, some of the sobering statistics include:

- Nearly half of female Alzheimer’s caregivers rate the emotional stress of Alzheimer’s disease at the highest possible level.
- Approximately a third of women caregivers are caring for someone 24/7, and almost half of women caregivers are providing more than 40 hours a week of care for an individual with Alzheimer’s.
- Four out of 10 caregivers say they had no choice in becoming caregivers. Six out of 10 women say they became caregivers because they lack other family to do it, and approximately 40 percent of women say they became caregivers because they are the only women in their families.
- One-third of female Alzheimer’s and dementia caregivers are part of the “sandwich generation” with children or grandchildren under the age of 18 living in their homes.
- Roughly a quarter of female caregivers made a promise to keep their loved ones out of an institution, but a third of women think that promise is too difficult to keep.

For more information, visit www.alz.org. “Reprinted by permission of the Alzheimer’s Association

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HELP STAMP OUT ALZHEIMER’S!

Every 68 seconds another American is diagnosed with Alzheimer’s, a fatal disease with no known cure or prevention. One out of 8 Americans age 65 and older will be affected by this disease. Last May resolutions were introduced to create a postage stamp (like the Breast Cancer research stamp which has raised over $80 million to defeat Breast Cancer) that would raise money for Alzheimer’s research. The Alzheimer’s stamp is a highly symbolic & therefore important piece of legislation that would allow ordinary citizens to show their support for individuals and families impacted by this devastating disease. Most importantly, it would help raise much needed funds for research through the voluntary purchase of postage stamps. Without congressional cosponsors, the resolutions will die in committee. Please call the US Capitol Switchboard at 202-224-3121 and ask to speak to your Congressman and Senators (Check the link below to identify who they are.) and tell them that you are counting on their support for the fundraising stamp and want them to sign on as a co-sponsor to House Res. 351 and Senate Res. 176. Please call and share this with all of your friends. Thank you.

www.contactingthecongress.org
Resveratrol for Alzheimer’s – Recruiting volunteers in mid May

Resveratrol
for Alzheimer’s Disease

ADCS Trials Enrolling...

**Nerve Growth Factor Study (NGF)**

The NGF is a Phase II clinical study of Ceregene’s CERE-110, a gene therapy product designed to deliver nerve growth factor (NGF) to the brain for the treatment of Alzheimer’s disease (AD) is currently underway. This study is a randomized, double-blind, placebo-controlled trial and employs gene therapy to deliver nerve growth factor (NGF) directly into the brain.

http://adcs.org/Studies/NGF.aspx

**ADNI II Study**

The goal of the Alzheimer’s Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer’s disease in future generations. Information from the study might, in the future, lead to new treatments.

http://adcs.org/Studies/ImagineADNI2.aspx

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