By Doug Bennett
University of Florida Health

University of Florida Health researchers have uncovered more evidence of a link between the brain’s stress response and a protein related to Alzheimer’s disease.

The research, conducted on a mouse model and in human cells, found that a stress-coping hormone released by the brain boosts the production of protein fragments. Those protein pieces, known as amyloid beta, clump together and trigger the brain degeneration that leads to Alzheimer’s disease.

The findings were published recently in The EMBO Journal by a group that includes Todd Golde, M.D., Ph.D., director of the UF Center for Translational Research in Neurodegenerative Disease and a professor in the UF College of Medicine’s department of neuroscience.

The research contributes to further understanding the potential relationship between stress and Alzheimer’s disease, a disorder believed to stem from a mix of genetic, lifestyle and environmental factors. The findings strengthen the idea of a link between stress and Alzheimer’s disease, Golde said.

“It adds detailed insight into the stress mechanisms that might promote at least one of the Alzheimer’s pathologies,” Golde said.

Figuring out the non-genetic factors that heighten the risk of Alzheimer’s disease is especially challenging, and the recent study is one step in a long process of looking at the effects of stress and other environmental factors, according to Golde. It could also point the way to a novel treatment approach in the future, he said.

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Stress and AD.....

Here is what researchers found: Stress causes the release of a hormone called corticotrophin releasing factor, or CRF, in the brain. That, in turn, increases production of amyloid beta. As amyloid beta collects in the brain, it initiates a complex degenerative cascade that leads to Alzheimer’s disease.

During laboratory testing, mouse models that were exposed to acute stress had more of the Alzheimer’s-related protein in their brains than those in a control group, researchers found. The stressed mice also had more of a specific form of amyloid beta, one that has a particularly pernicious role in the development of Alzheimer’s disease.

To better understand how CRF increases the amount of Alzheimer’s-related proteins, researchers then treated human neurons with CRF. That caused a significant increase in the amyloid proteins involved in Alzheimer’s disease.

Those and other complex experiments reveal more about the mechanics of a likely relationship between stress and Alzheimer’s disease. The stress hormone, CRF, causes an enzyme known as gamma secretase to increase its activity. That, in turn, causes more of the Alzheimer’s-related protein to be produced, Golde said.

Modifying environmental factors such as stress is yet another approach to warding off Alzheimer’s disease, and one that is easier than modifying the genes that cause the disorder, Golde said. One possible solution — blocking the CRF receptor that initiates the stress-induced process that generates Alzheimer’s-related proteins — didn’t work. Researchers are now looking at an antibody that could be used to block the stress hormone directly, Golde said.

“These softer, non-genetic factors that may confer risk of Alzheimer’s disease are much harder to address,” Golde said. “But we need more novel approaches in the pipeline than we have now.”

The idea of looking more closely at the mechanism linking stress and Alzheimer’s disease came from Seong-Hun Kim, M.D., Ph.D., a former assistant professor in the College of Medicine’s department of pharmacology and therapeutics and now a psychiatrist in Seattle. Much of the project’s experiments were done by Hyo-Jin Park, Ph.D., who was a postdoctoral associate during the project and is now an assistant scientist in the College of Medicine’s department of aging and geriatric research. Kevin Felsenstein, Ph.D., an associate professor of neuroscience in UF’s College of Medicine, also made major contributions to the work.

The research was supported by multiple grants from the National Institutes of Health and the U.S. Department of Veterans Affairs.
More than five million Americans are living with Alzheimer’s disease (AD). Of them, 400,000 also have Down syndrome. Both groups have similar looking brains with higher levels of the protein beta amyloid. In fact, patients with Down syndrome develop the abnormal protein at twice the rate. Results of a pilot study, published in the September issue of *Frontiers in Behavioral Neuroscience*, confirms the pathogenic role of beta amyloid in dementia as seen in both AD and Down syndrome.

“People with Down syndrome represent the world’s largest population of predeter-mined Alzheimer’s disease. By studying these individuals, we can develop insights into how Alzheimer’s disease naturally progresses and potential drug targets,” said principal investigator Michael Rafii, MD, PhD, assistant professor of neurosciences and interim co-director of the Alzheimer’s Disease Cooperative Study (ADCS) at UC San Diego.

The 3-year study, called the Down Syndrome Biomarker Initiative (DSBI), involved twelve participants between the ages of 30 and 60 with Down syndrome, to study their aging process. The study focused on how soon protein plaques developed, where in the brain they were located and the effects of the plaques on cognition. To quantify how much amyloid was present in the brain, the study included extensive neuroimaging such as volumetric MRI, amyloid PET, FDG PET, and retinal amyloid imaging.

“This study shows some of the earliest known Alzheimer’s disease biomarker changes in adults with Down syndrome and underscores the need for additional studies,” said Rafii. “This study will set the stage for the first clinical trial of anti-beta amyloid therapy in the preclinical treatment of Alzheimer’s disease in adults with Down syndrome.”

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AD is believed to occur from the toxic buildup of beta amyloid. There are many forms of AD that are genetically inherited, including Down syndrome. People with Down syndrome have an extra copy of the 21st chromosome where the production gene for the beta amyloid protein resides.

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Resveratrol Impacts Alzheimer’s Disease Biomarker

By Karen Teber, Georgetown University Medical Center

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The largest nationwide clinical trial to study high-dose resveratrol long-term in people with mild to moderate Alzheimer’s disease found that a biomarker that declines when the disease progresses was stabilized in people who took the purified form of resveratrol.

Resveratrol is a naturally occurring compound found in foods such as red grapes, raspberries, dark chocolate and some red wines.

The results, published online today in Neurology, “are very interesting,” says the study’s principal investigator, R. Scott Turner, MD, PhD, director of the Memory Disorders Program at Georgetown University Medical Center (pictured). Turner, who treats patients at MedStar Georgetown University Hospital, cautions that the findings cannot be used to recommend resveratrol. “This is a single, small study with findings that call for further research to interpret properly.”

The resveratrol clinical trial was a randomized, phase II, placebo-controlled, double blind study in patients with mild to moderate dementia due to Alzheimer’s disease. An “investigational new drug” application was required by the U.S. Food and Drug Administration to test the pure synthetic (pharmaceutical-grade) resveratrol in the study. It is not available commercially in this form.

The investigators enrolled 119 participants for the one-year study. The highest dose of resveratrol tested was one gram by mouth twice daily — equivalent to the amount found in about 1,000 bottles of red wine.

Patients who were treated with increasing doses of resveratrol over 12 months showed little or no change in amyloid-beta40 (Abeta40) levels in blood and cerebrospinal fluid. In contrast, those taking a placebo had a decrease in the levels of Abeta40 compared with their levels at the beginning of the study.

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“A decrease in Abeta40 is seen as dementia worsens and Alzheimer’s disease progresses; still, we can’t conclude from this study that the effects of resveratrol treatment are beneficial,” Turner explains. “It does appear that resveratrol was able to penetrate the blood brain barrier, which is an important observation. Resveratrol was measured in both blood and cerebrospinal fluid.”

John Bozza, 80, participated in the study. Five years ago, his wife, Diana, began noticing “something wasn’t quite right.” He was diagnosed with mild cognitive impairment, but only a year later, his condition progressed to mild Alzheimer’s.

Diana, whose twin sister died from the same disease, says there are multiple reasons she and John decided to participate in the resveratrol study, and they now know he was assigned to take the active drug.

“I definitely want the medical community to find a cure,” she says. “And of course I thought there’s always a chance that John could have been helped, and who knows, maybe he was.”

The researchers studied resveratrol because it activates proteins called sirtuins, the same proteins activated by caloric restriction. The biggest risk factor for developing Alzheimer’s is aging, and studies with animals found that most age-related diseases—including Alzheimer’s—can be prevented or delayed by long-term caloric restriction (consuming two-thirds the normal caloric intake).

Turner says the study also found that resveratrol was safe and well tolerated. The most common side effects experienced by participants were gastrointestinal-related, including nausea and diarrhea. Also, patients taking resveratrol experienced weight loss while those on placebo gained weight.

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One outcome in particular was confounding, Turner notes. The researchers obtained brain MRI scans on participants before and after the study, and found that resveratrol-treated patients lost more brain volume than the placebo-treated group.

“We’re not sure how to interpret this finding. A similar decrease in brain volume was found with some anti-amyloid immunotherapy trials,” Turner adds. A working hypothesis is that the treatments may reduce inflammation (or brain swelling) found with Alzheimer’s.

The study, funded by the National Institute on Aging and conducted with the Alzheimer’s Disease Cooperative Study, began in 2012 and ended in 2014. GUMC was one of 21 participating medical centers across the U.S.

Further studies, including analysis of frozen blood and cerebrospinal fluid taken from patients, are underway to test possible drug mechanisms.

“Given safety and positive trends toward effectiveness in this phase 2 study, a larger phase 3 study is warranted to test whether resveratrol is effective for individuals with Alzheimer’s — or at risk for Alzheimer’s,” Turner says.

Resveratrol and similar compounds are being tested in many age-related disorders including cancer, diabetes and neurodegenerative disorders. The study Turner led, however, is the largest, longest and highest dose trial of resveratrol in humans to date.

The research was supported by a grant from the National Institute on Aging (U01 AG010483). Turner reports no personal financial interests related to the study.
Atrial Fibrillation in Middle Age
Ups Dementia Risk

Add another notch to the evidence that an unhealthy heart can harm the brain. In the September 21 JAMA Neurology, researchers led by M. Arfan Ikram of Erasmus Medical Center in Rotterdam, the Netherlands, report that having atrial fibrillation, a common cardiovascular disease in older adults, was associated with an elevated risk of developing dementia over the next 20 years. The link was particularly strong for middle-aged participants, fueling a trend in epidemiology that cardiovascular health in midlife influences brain health in old age. “This highlights the fact that prevention needs to start years or decades before people develop cognitive symptoms,” co-author Frank Wolters told Alzforum. It is not yet clear, however, what type of treatment for this heart condition would most lower dementia risk.

“Their study clearly adds to the growing body of evidence that atrial fibrillation is a significant risk factor for dementia,” Jared Bunch at the Intermountain Medical Center Heart Institute, Murray, Utah, wrote to Alzforum.

Atrial fibrillation is an abnormal heart rhythm in which the upper chambers flutter irregularly, reducing blood flow. The heart can be coaxed back into normal rhythm with drugs or shocked with electricity, but the condition often recurs and persists. In people with the disease, the heart’s ineffective pumping can cause blood to clot, raising the risk of stroke. Thus, patients are often treated with anticoagulants. Notably, even tiny strokes or clotted matter in the blood can precipitate cognitive decline and dementia.

The connection between atrial fibrillation and stroke suggested to many researchers that the condition might also be a risk factor for dementia, but previous studies examining this have yielded mixed results. Some papers reported a link with Alzheimer’s disease, as well as vascular dementia, especially in people under 70. Other studies, mostly in people over 75, found no association. An early study in the Rotterdam cohort supported a link, but because participants were not followed over time, the researchers could not infer that the cardiac condition caused cognitive decline.

To parse this out, first author Renée de Bruijn followed 6,514 cognitively normal participants in the Rotterdam Study who were 55 or older at baseline. About 5 percent had an initial diagnosis of atrial fibrillation, and another 12 percent developed the condition during the 20 years of the study. Overall, about 15 percent of the population developed dementia. Having atrial fibrillation increased the risk by about one-third, regardless of whether people also had a stroke.

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Atrial Fibrillation and Dementia cont’d.....

However, it turned out that the association was driven by the younger members of the cohort. Among people under the population’s median age of 67, having atrial fibrillation nearly doubled dementia risk. Moreover, among this group, the longer a person had this heart problem, the higher their dementia risk rose. Those who had an atrial fibrillation diagnosis for more than 12 years tripled their risk of dementia. By contrast, among the older participants, atrial fibrillation did not significantly bump up risk, and there was no relationship with the length of time they had the condition.

Atrial fibrillation may be a stronger risk factor in younger people because they have more years to accumulate brain damage, Wolters suggested. Other recent studies have reported that cardiac and metabolic health in middle age—but not old age—influence later cognitive decline. Meta-analyses of these risk factors also support a midlife connection.

Does atrial fibrillation predispose to vascular dementia, or to AD specifically? In this study, 80 percent of the dementia cases were clinically diagnosed as Alzheimer’s according to older National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria, but most were not confirmed by autopsy or amyloid imaging.

The finding hints that atrial fibrillation could be a risk factor for AD, though the mechanism remains a mystery. Dementia risk occurred independently of stroke in this cohort, but the authors noted that mini-strokes may have gone undetected and could have hastened cognitive decline. Chronic atrial fibrillation also could have lowered blood flow to the brain. Several previous studies have tied vascular health to amyloid deposition.

Could optimal treatment of atrial fibrillation prevent dementia? The authors could not address that because they had no data on how often or for how long participants had active fluttering of the heart, nor what treatments they took. “Future studies should examine the impact of different types of treatment for atrial fibrillation and whether they reduce the risk of cognitive decline. That will be vital for prevention,” Wolters said.—Madolyn Bowman Rogers
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/clinalResearchStudy.aspx

NOBLE A Study for People with Mild to Moderate Alzheimer’s Disease

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease
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