Anti-inflammatory Protein May Trigger Plaques in Alzheimer’s

By Morgan Sherburne, University of Florida, College of Medicine

Inflammation has long been studied in Alzheimer’s, but in a counterintuitive finding reported in a new paper, University of Florida researchers have uncovered the mechanism by which anti-inflammatory processes may trigger the disease.

This anti-inflammatory process might actually trigger the build-up of sticky clumps of protein that form plaques in the brain. These plaques block brain cells’ ability to communicate and are a well-known characteristic of the illness.

The finding suggests that Alzheimer’s treatments might need to be tailored to patients depending on which forms of Apolipoprotein E, a major risk factor for Alzheimer’s disease, these patients carry in their genes.

The researchers have shown that the anti-inflammatory protein interleukin 10, or IL-10, can actually increase the amount of apolipoprotein E, or APOE, protein — and thereby plaque — that accumulates in the brain of a mouse model of Alzheimer’s, according to the study, published online Jan. 22 in the journal Neuron.

In the 1990s, researchers theorized that using nonsteroidal anti-inflammatory drugs, or NSAIDs, might protect people from the onset of Alzheimer’s by dampening inflammation that released a cascade of harmful proteins. Though NSAIDs were shown to be effective in some studies, other research that evaluated a group of participants taking NSAIDs over time failed to show any clear protective benefit.

“There are many different kinds of NSAIDs,” said Todd Golde, M.D., Ph.D., director of the Center for Translational Research in Neurodegenerative Disease and the paper’s lead author. “Not all NSAIDs are equal, and it wasn’t clear what else they were doing when they were addressing their intended target.”
Previously, researchers hypothesized that a flood of proteins, called cytokines, involved in promoting inflammation in the brain contributed to the formation of plaque in Alzheimer’s disease. However, in this publication, the UF researchers provide new evidence that anti-inflammatory stimuli may actually increase plaque.

“This is another piece of evidence that overturns the long-held hypothesis that a ‘cytokine storm’ creates a self-reinforcing, neurotoxic feedback loop that promotes amyloid-beta (plaque) deposition,” said Paramita Chakrabarty, Ph.D., a member of the UF Center for Translational Research in Neurodegenerative Disease, an assistant professor in the UF College of Medicine department of neuroscience and the paper’s co-author.

The researchers said that a person’s risk of developing Alzheimer’s hinges on the relationship between IL-10 and APOE. APOE clears the cell of many different proteins, including the protein amyloid-beta, which contributes to the buildup of plaque. But there are several different forms of APOE in cells, which differ from each other by only one or two amino acids. The form called APOE4 is the largest known genetic risk factor in Alzheimer’s disease, while APOE2 is thought to be protective, Golde said.

“About 15 to 17 percent of the population has the APOE 4 allele, and about 50 percent of people with Alzheimer’s have it,” Golde said.

In this case, the authors showed that the anti-inflammatory protein IL-10 actually increases levels of all types of mouse APOE, which resembles human APOE. In the mouse model, APOE binds with amyloid-beta rather than clearing it from the brain, accelerating buildup of plaque in the brain of a mouse with Alzheimer’s. How an anti-inflammatory therapy based on IL-10 expression might alter risk for Alzheimer’s may depend on the genetic variant of APOE protein the person is carrying. If the person has an APOE4 allele the researchers predict the risk for Alzheimer’s would increase.

“In one way, this study offers additional insight into how environmental influences interacts with people’s underlying genotypes to alter their risk for diseases,” Golde said. “We know that people are exposed to various inflammatory or anti-inflammatory stimuli throughout their lives. Depending on what their genotype is, that exposure may in some cases protect them from Alzheimer’s, or, in other cases, increase their risk for Alzheimer’s.”

The research was funded in part through an $8.4 million grant to speed up the process of finding therapies for Alzheimer’s disease from the National Institutes of Health’s Office of the Director, with additional funding from the National Institute on Aging and the Ellison Medical Foundation. Next, the researchers plan to carry out more thorough and mechanistic studies to exactly understand how an increase in APOE protein induced by IL-10 will affect amyloid plaque deposition in mice carrying different alleles of human APOE.
SuperAger Brains Yield New Clues to Their Remarkable Memories

By Marla Paul, Northwestern University

CHICAGO – SuperAgers, aged 80 and above, have distinctly different looking brains than those of normal older people, according to new Northwestern Medicine® research that is beginning to reveal why the memories of these cognitively elite elders don’t suffer the usual ravages of time. SuperAgers have memories that are as sharp as those of healthy persons decades younger. Understanding their unique “brain signature” will enable scientists to decipher the genetic or molecular source and may foster the development of strategies to protect the memories of normal aging persons as well as treat dementia. Published Jan. 28 in the Journal of Neuroscience, the study is the first to quantify brain differences of SuperAgers and normal older people.

Cognitive SuperAgers were first identified in 2007 by scientists at Northwestern’s Cognitive Neurology and Alzheimer’s Disease Center at Northwestern University Feinberg School of Medicine.

Their unusual brain signature has three common components when compared with normal persons of similar ages: a thicker region of the cortex; significantly fewer tangles (a primary marker of Alzheimer’s disease) and a whopping supply of a specific neuron --von Economo-- linked to higher social intelligence.

“The brains of the SuperAgers are either wired differently or have structural differences when compared to normal individuals of the same age,” said Changiz Geula, study senior author and a research professor at the Cognitive Neurology and Alzheimer’s Disease Center. “It may be one factor, such as expression of a specific gene, or a combination of factors that offers protection.”

The Center has a new NIH grant to continue the research.

“Identifying the factors that contribute to the SuperAgers’ unusual memory capacity may allow us to offer strategies to help the growing population of ‘normal’ elderly maintain their cognitive function and guide future therapies to treat certain dementias,” said Tamar Gefen, the first study author and a clinical neuropsychology doctoral candidate at Feinberg.
MRI imaging and an analysis of the SuperAger brains after death show the following brain signature:

1) MRI imaging showed the anterior cingulate cortex of SuperAgers (31 subjects) was not only significantly thicker than the same area in aged individuals with normal cognitive performance (21 subjects), but also larger than the same area in a group of much younger, middle-aged individuals (ages 50 to 60, 18 subjects). This region is indirectly related to memory through its influence on related functions such as cognitive control, executive function, conflict resolution, motivation and perseverance.

2) Analysis of the brains of five SuperAgers showed the anterior cingulate cortex had approximately 87 percent less tangles than age-matched controls and 92 percent less tangles than individuals with mild cognitive impairment. The neurofibrillary brain tangles, twisted fibers consisting of the protein tau, strangle and eventually kill neurons.

3) The number of von Economo neurons was approximately three to five times higher in the anterior cingulate of SuperAgers compared with age-matched controls and individuals with mild cognitive impairment.

“It’s thought that these von Economo neurons play a critical role in the rapid transmission of behaviorally relevant information related to social interactions,” Geula said, “which is how they may relate to better memory capacity.” These cells are present in such species as whales, elephants, dolphins and higher apes.

Other Northwestern authors on the study include Melanie Peterson, Steven T. Papastefan, Adam Martersteck, Kristen Whitney, Alfred Rademaker, Eileen Bigio, Sandra Weintraub, Emily Rogalski and Dr. M. Marsel Mesulam.

The research was funded by National Institute on Aging, National Institutes of Health grant AG045571, The Davee Foundation, the Northwestern University Alzheimer’s Disease Core Center grant AG13854 from the National Institute on Aging, a fellowship from the National Institute on Aging grant F31-AG043270 and others.

For more information on the SuperAger study, call 312-503-2716 or at email agingresearch@northwestern.edu.
Curcumin’s Ability to Fight Alzheimer’s Studied

by Patricia Jumbo-Lucioni, Vanderbilt University

One of the most promising new treatments for Alzheimer’s disease may already be in your kitchen. Curcumin, a natural product found in the spice turmeric, has been used by many Asian cultures for centuries, and a new study indicates a close chemical analog of curcumin has properties that may make it useful as a treatment for the brain disease.

“Curcumin has demonstrated ability to enter the brain, bind and destroy the beta-amyloid plaques present in Alzheimer’s with reduced toxicity,” said Wellington Pham, Ph.D., assistant professor of Radiology and Radiological Sciences and Biomedical Engineering at Vanderbilt and senior author of the study, published recently in the Journal of Alzheimer’s Disease.

Accumulation and aggregation of protein fragments, known as beta-amyloid, drives the irreversible loss of neurons in Alzheimer’s disease.

Developing small molecules to reduce this accumulation or promote its demolition is crucial, but the ability of these small molecules to cross the blood-brain barrier has been a restricting factor for drug delivery into the brain.

Pham and colleagues at Shiga University of Medical Science in Otsu, Japan, developed a new strategy to deliver a molecule similar to curcumin more effectively to the brain.

“One of the difficulties in the treatment of Alzheimer’s disease is how to deliver drugs across the blood brain barrier,” he said. “Our body has designed this barrier to protect the brain from any toxic molecules that can cross into the brain and harm neurons.

“But it is also a natural barrier for molecules designed for disease-modifying therapy,” Pham said.

To work around the problems of giving the drug intravenously, the researchers decided to develop an atomizer to generate a curcumin aerosol. The Japanese researchers developed a molecule similar to curcumin, FMeC1, which was the one used in this study.

“The advantage of the FMeC1 is that it is a perfluoro compound, which can be tracked by the biodistribution in the brain noninvasively using magnetic resonance imaging. Curcumin is a very simple chemical structure, so it is not expensive to generate the analog,” Pham said. “In this way the drug can be breathed in and delivered to the brain,” he said, noting that nebulizers are out in the market already, and are relatively inexpensive. “In this paper we also showed that delivery to the cortex and hippocampal areas is more efficient using aerosolized curcumin than intravenous injection in a transgenic mouse model of Alzheimer’s disease.”
Prostate Cancer Drug Slows Memory Loss in Women with Alzheimer's Disease

By Susan Lampert Smith, University of Wisconsin-Madison

Madison, Wisconsin - Women with Alzheimer’s disease showed stable cognition for a year when a drug that is more commonly used to treat advanced prostate cancer was added to their drug regimen, according to a new study from researchers at the University of Wisconsin-Madison.

“This is the first time any therapy has been shown to stabilize memory loss over a year,” says Dr. Craig Atwood, co-lead author of the study and associate professor of medicine at the UW School of Medicine and Public Health.

Researchers are testing new and repurposed drugs with different mechanisms of action. Unlike atypical antipsychotics, which block dopamine receptors, the new compounds act on serotonin, acetylcholine, and norepinephrine. In Alzheimer’s, these neurotransmitter systems malfunction, Abushakra said. Acetylcholine transmission drops the most, by 50 to 85 percent, but serotonin, dopamine, and norepinephrine signaling are also suppressed. Paul Rosenberg of Johns Hopkins noted that neurotransmission goes haywire in patterns that correspond to particular psychiatric symptoms. For example, in agitated patients, hippocampal serotonin falls while dopamine turnover in the cerebellum rises. The hope is that the new drugs may help to restore balance to brain signaling, speakers said.

The study was published January 20th, 2014 in the Journal of Alzheimer’s Disease.

The clinical trial, initiated by Dr. Richard Bowen at the former Voyager Pharmaceutical Corporation, followed 109 women with mild to moderate Alzheimer’s disease. Some were treated with the drug leuprolide acetate (Lupron Depot), used to treat cancer in men and severe endometriosis in women, and with an acetylcholineesterase inhibitor such as Aricept, which improves mood in people with the condition but does little to slow memory loss. Others taking an acetylcholineesterase inhibitor received low-dose Lupron alone or a placebo.

It found that the women treated with both Aricept and high-dose Lupron Depot had almost no decline (0.18 points) in their scores on the ADAS-cog, a test of memory, compared with declines of 4.21 for those taking an acetylcholinesterase inhibitor and low-dose Lupron and 3.3 in those only taking an acetylcholinesterase inhibitor after one year.

Atwood explained that earlier epidemiological studies involving hundreds of thousands of patients had found that men who had prostate disease and were treated with Lupron had a 34 to 55 percent decreased risk of developing Alzheimer’s disease compared with prostate-cancer patients who didn’t receive the drug.

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Prostate Cancer Drug cont’d.......... 

He explained that Lupron acts to suppress gonadotropin-releasing hormone (GnRH), which is produced in the brain and controls ovulation in women and spermatogenesis in men. This in turn decreases the production of gonadotropins, hormones that regulate the synthesis of sex steroids like estrogen and testosterone.

For these reasons, it is also used to treat estrogen-sensitive breast cancer, endometriosis, and premature puberty. Decreasing GnRH and gonadotropins with Lupron prevents some of the negative effects of elevated GnRH and gonadotropins on the brain, which occurs following menopause.

Post-menopausal women were chosen for this study because they no longer produce sex steroids; men could have been affected by the loss of testosterone caused by the Lupron.

“This promising combination therapy (acetylcholineesterase inhibitors and Lupron Depot) warrants testing in early and late stages of Alzheimer’s disease,” Atwood says. “However, since the company that performed this study is now out of business, it remains to be seen whether this therapy will ever be tested in further clinical trials and reach the market.”

Country Singer Wins Grammy for Song about Alzheimer’s

For country music fans it came as no surprise that 78 year-old Glen Campbell, the iconic and highly-celebrated country musician, won Best Country Song at the 2015 Grammy Awards. But for those fans and others it was the subject matter of the song that came as a shock. Campbell is in the late stages of Alzheimer’s and living in a long-term care facility for Alzheimer’s patients. He co-wrote ‘I’m Not Gonna Miss You’ with Julian Raymond while he was still lucid enough to form the words and melody. The song was featured in “Glen Campbell: I’ll Be Me”, a documentary that follows Campbell’s journey through Alzheimer’s. The bittersweet love song chronicles his battle with Alzheimer’s and his affection for his family. The ode to Alzheimer’s is both poignant and moving; Campbell performed it on stage numerous times during his final concert tour, two years ago. Unable to attend the Grammys, his wife Kim accepted his award. He was diagnosed in 2011. The song was also nominated for an Oscar Award for Best Original Song at this year’s Academy Awards. A video of the song can be viewed here: http://tinyurl.com/l96u2hy

Actress in Film About Early AD Wins an Oscar

Actress Julianne Moore won the 2015 Best Actress Oscar for her Still Alice portrayal of Alice Howland, a college professor diagnosed with early-onset Alzheimer's. The movie is based on the fictional book of the same name by Lisa Genova, a Harvard neuroscientist. The book was published in 2009.
University of Southern California (USC) neuroscientists may have unlocked another puzzle to preventing risks that can lead to Alzheimer's disease. Researchers at Keck Medicine of USC used high-resolution imaging of the living human brain to show for the first time that the brain's protective blood barrier becomes leaky with age, starting at the hippocampus, a critical learning and memory center that is damaged by Alzheimer's disease.

The study indicates it may be possible to use brain scans to detect changes in blood vessels in the hippocampus before they cause irreversible damage leading to dementia in neurological disorders characterized by progressive loss of memory, cognition and learning. These findings would have broad implications on conditions that will affect 16 million Americans over age 65 by 2050, according to the latest figures from the Alzheimer's Association. The research appears in the Jan. 21, 2015, edition of the peer-reviewed scientific journal *Neuron*.

"This is a significant step in understanding how the vascular system affects the health of our brains," said Berislav V. Zlokovic, M.D., Ph.D., director of the Zilkha Neurogenetic Institute (ZNI) at the Keck School of Medicine, the Mary Hayley and Selim Zilkha Chair for Alzheimer's Disease Research and the study's principal investigator. "To prevent dementias including Alzheimer's, we may need to come up with ways to reseal the blood-brain barrier and prevent the brain from being flooded with toxic chemicals in the blood. Pericytes are the gate-keepers of the blood-brain barrier and may be an important target for prevention of dementia."

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Alzheimer’s disease is the most common type of dementia, a general term for loss of memory and other mental abilities. According to the Alzheimer's Association, roughly 5.2 million people of all ages in the United States today have Alzheimer's disease, an irreversible, progressive brain disease that causes problems with memory, thinking and behavior. Post-mortem studies of brains with Alzheimer’s disease show damage to the blood-brain barrier, a cellular layer that regulates entry of blood and pathogens into the brain. The reasons why and when this damage occurs, however, remain unclear.

In the Neuron study, Zlokovic's research team examined contrast-enhanced brain images from 64 human subjects of various ages and found that early vascular leakage in the normally aging human brain occurs in the hippocampus, which normally shows the highest barrier properties compared to other brain regions. The blood-brain barrier also showed more damage in the hippocampal area among people with dementia than those without dementia, when controlling for age.

To validate the research method, the USC team examined brain scans of young people with multiple sclerosis without cognitive impairment, finding no difference in barrier integrity in the hippocampus between those of the same age with and without the disease. The researchers also looked at the subjects' cerebrospinal fluid (CSF), which flows through the brain and spinal cord. Individuals who showed signs of mild dementia had 30 percent more albumin, a blood protein, in their CSF than age-matched controls, further indicating a leaky blood-brain barrier. The CSF of individuals with dementia also showed a 115 percent increase of a protein related to pericyte injury. Pericytes are cells that surround blood vessels and help maintain the blood brain barrier; previous research has linked pericytes to dementia and aging.

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Study participants were recruited through the USC Alzheimer's Disease Research Center and Huntington Medical Research Institute. Other USC co-authors include Axel Montagne, Melanie D. Sweeney, Matthew R. Halliday, Abhay P. Sagare, Zhen Zhao, Arthur W. Toga, Collin Y. Liu, Lilyana Amezcua, Helena C. Chui and Meng Law. The study was supported by various National Institutes of Health agencies (grants R37NS34467, R37AG23084, R01AG039452, R21EB013456, UL1TR000130, P50AG05142, 7P41EB015922, EB000993), the Zilkha Senior Scholar program and L. K. Whittier Foundation.
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

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

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

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

On a temporary enrollment hold until further notice:
SNIFF – the Study of Nasal Insulin to Fight Forgetfulness
The **CONNECT** study will test whether an oral, experimental drug, AZD0530 (saracatinib), will slow progression in mild-stage Alzheimer’s disease (AD). Although the cause of AD is unknown, several lines of evidence suggest that a peptide known as beta-amyloid plays a central role. Convergent evidence in recent years has yielded a refinement of the “amyloid hypothesis”, suggesting that neurotoxicity of beta-amyloid oligomers leads to Alzheimer’s disease. The protein Fyn kinase, a member of the Src family kinases, may play a fundamental role in the pathway by which beta-amyloid oligomers damage neurons. AZD0530 is a selective inhibitor of Src family kinases that was previously developed as a cancer therapy, but may hold greater promise as a treatment for AD. **CONNECT** researchers will use PET imaging to evaluate whether the drug is effective in slowing decline in brain metabolism and will also determine whether it is safe and well tolerated in patients with AD. The study is currently enrolling at Yale University and will begin enrolling at additional sites in the near future.

For more information please visit:

[http://adcs.org/Studies/Connect.aspx](http://adcs.org/Studies/Connect.aspx)