Subtracting Gravity from Alzheimer's

Alzheimer’s disease is a global problem. In the United States alone, more than 5 million people have the disease and a new diagnosis is made every 67 seconds—numbers that are just a fraction of worldwide totals. Among medical researchers, Alzheimer’s is a top priority.

Researchers working with astronauts on the International Space Station are embarking on a mission to discover the origin of Alzheimer’s. Although the details are still a little fuzzy, researchers believe that Alzheimer’s and similar diseases advance when certain proteins in the brain assemble themselves into long fibers that accumulate and ultimately strangle nerve cells in the brain.

“They're sort of like the crankcase sludge of the human body,” explains Dan Woodard of NASA’s Kennedy Space Center. "The fibers are not active, ever because your body get rid of them."

These fibers take decades to form and accumulate—hence the link between Alzheimer’s and aging. In laboratories on Earth, researchers have figured out how to make protein fibers accumulate more quickly, so they can study the process without waiting so long. On the space station, accumulated fibers do not collapse under their own weight, which makes the station an even better place to study them.

A four-inch cube containing the experiment, which was selected in an ISS research contest by Space Florida and Nanoracks, and built at the Florida Institute of Technology, blasted off to the International Space Station onboard the SpaceX cargo resupply mission on Jan. 10th. The experiment itself, SABOL, or Self-Assembly in Biology and the Origin of Life: A Study into Alzheimer’s, will be fully automated.

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Gravity cont’d…..

However, observations from this experiment alone won’t lead directly to the discovery of a cure. SABOL is geared more towards understanding the way that Alzheimer’s progresses, not towards creating a pill to stop it from happening. Although this experiment is only the first in what will surely be a series, Woodard is optimistic that it could be an extremely valuable learning experience.

"Everybody wants a cure, but without knowing the actual cause of the disease, you're basically shooting in the dark," Woodard says. "We don't understand the true mechanism of the disease. If we're lucky, then we'll find out whether proteins will aggregate in space. Only in weightlessness can you produce an environment free of convection so you can see whether they form on their own. We expect to learn incrementally from this."

Eventually, projects like SABOL could lead to the discovery of a method to slow down the rate at which the harmful fibers grow, thereby opening a window for a cure. The results of the experiment will be seen after the samples are returned to Earth and are examined underneath an atomic force microscope. Woodard speculates that the cause of Alzheimer’s could surprise us by being deceptively simple.

Says Woodard, "There have to be chemicals or processes that hinder or encourage the growth of protein fibers. It may be something as simple as temperature or salt concentration of the fluid in the brain."

Strange but true: The key to unraveling the mysterious cause of Alzheimer’s disease may not lie in the recesses of the human brain, but rather in the weightless expanse of space. If an answer is ultimately found, it could very well spring from the microgravity of Earth’s orbit. The experiment begins soon.

To watch the video please visit: http://science.nasa.gov/science-news/science-at-nasa/2015/04mar_sabol/

Courtesy of NASA

Author: Rachel Molina | Production Editor: Dr. Tony Phillips
A study from researchers at Massachusetts General Hospital (MGH) and Brigham and Women’s Hospital (BWH) reveals for the first time exactly how mutations associated with the most common form of inherited Alzheimer’s disease produce the disorder’s devastating effects. Appearing in the March 4 issue of Neuron, the paper upends conventional thinking about the effects of Alzheimer’s-associated mutations in the presenilin genes and provides an explanation for the failure of drugs designed to block presenilin activity.

“Our study provides new insights into Alzheimer’s disease by showing how human mutations that cause the disease lead to neurodegeneration and dementia,” says Raymond J. Kelleher III, MD, PhD, of the MGH Department of Neurology and Center for Human Genetic Research, co-senior author of the Neuron paper. “We found that mutations in the presenilin-1 gene promote the hallmark features of the disease by decreasing, rather than increasing, function of the presenilin-1 protein and the gamma-secretase enzyme. In addition to the important therapeutic implications of our findings, we have also generated the first animal model in which an Alzheimer’s-disease-causing mutation produces neurodegeneration in the cerebral cortex.”

While inherited or familial Alzheimer’s disease (FAD) is very rare, accounting for only around 1 percent of cases, the identification more than 20 years ago of the genes that cause FAD provided the first clues into the mechanism behind the effects of the disease. The rarest FAD-associated mutations are found in the amyloid precursor protein (APP), which is clipped by multiple proteases to produce the beta-amyloid peptides that accumulate into the amyloid plaques characteristic of the disease. Mutations in two presenilin genes – which encode essential components of gamma-secretase, one of the proteases that process APP – account for around 90 percent of FAD cases. Individuals with presenilin-associated FAD develop Alzheimer’s symptoms even earlier than those with APP mutations.
While the mechanism by which presenilin mutations cause neurodegeneration has not been known, the general thinking was that they increase presenilin and gamma secretase activity, resulting in overproduction of beta-amyloid and particularly of beta-amyloid 42, which is thought to be more prone to deposition in plaques. As a result, development of gamma secretase inhibitors has been a major therapeutic effort pursued by pharmaceutical companies. But Jie Shen, PhD, of the Ann Romney Center for Neurologic Diseases at BWH, co-senior author of the Neuron paper, questioned this widely held view and the use of gamma secretase inhibitors to treat Alzheimer’s disease because her earlier investigations into the normal function of the presenilin genes showed that genetically suppressing presenilin and gamma secretase activity in adult mice caused Alzheimer’s-like neurodegeneration, results that contrasted with those of studies in which the overproduction of beta-amyloid or presenilins failed to produce neurodegeneration.

In a 2007 paper published in PNAS, Shen and Kelleher – who had been treating FAD patients with mutations in the presenilin-1 gene and researching brain mechanisms underlying cognitive function – proposed what they termed the presenilin hypothesis: that a loss of presenilin function may be the primary event triggering neurodegeneration and dementia in FAD. In recent studies, Kelleher identified a novel FAD-causing presenilin-1 mutation that inactivated its function in a sensitive cell culture system. In collaboration with Shen, his group went on to show that a series of FAD mutations all impaired presenilin-1 function in cell culture.

These findings raised the pivotal question of how such mutations affected presenilin-1 function in living animals, especially in the brain. While Shen’s earlier investigations had used strains of mice in which one or more copies of the presenilin genes were totally inactivated, for this study she and Kelleher generated mice in which specific, FAD-associated presenilin-1 mutations were “knocked in” to the gene, causing them to be expressed just as they are in human patients with that particular mutation. One of the mutations they tested is relatively common among FAD patients, while the other is fairly rare; and both are located near the site where the protein interacts with its target molecules, when incorporated into gamma secretase.

As was the case with animals in which both copies of presenilin-1 were deleted in earlier studies, those in which both copies were mutated did not survive after birth. Mice in which a single presenilin-1 gene was mutated survived, but showed deficiencies in learning and memory compared with control mice. Production of beta-amyloid within the brains of these mice was actually reduced, although the ratio between forms of the peptide was changed, with proportionally more plaque-associated beta-amyloid 42 being generated. Closer examination of the brains of mice with the FAD mutation showed the same sort of synaptic dysfunction and age-associated neurodegeneration seen in the brains of patients with Alzheimer’s disease.
This paper clearly shows that these FAD mutations cause a loss of presenilin function and gamma secretase activity, leading to the loss of neurons in the adult brain,” says Shen. “The most important implication of our findings is that strategies that enhance rather than inhibit gamma secretase should be investigated as potential Alzheimer’s therapies. They also may explain why a major clinical trial of a gamma secretase “inhibitor failed to help patients and actually worsened their cognitive abilities.” She adds that their presenilin hypothesis does not rule out a role for beta-amyloid in Alzheimer’s pathology, it just places presenilin/gamma secretase activity closer to the pathway that leads to neurodegeneration.

While this study only examined presenilin-1 mutations, Kelleher notes, the researchers believe that loss of function is a general property of FAD mutations in both presenilin genes. Investigation of the mechanisms underlying the effects of the APP mutations is also warranted, as is examination of how presenilin dysfunction may contribute to the common, late-onset form of Alzheimer’s disease. “Shared or convergent molecular pathways may be responsible for pathogenesis in both familial and sporadic forms, and we hope that mechanistic relationships will become clearer with the identification of genetic risk factors for sporadic or late-onset Alzheimer’s disease,” he says. “We’re now actively pursuing strategies to develop candidate therapies that restore presenilin-1 function. We also hope that our knockin mouse model will facilitate development and preclinical testing of these and other agents that can combat neurodegeneration in Alzheimer’s disease.”

Kelleher is an assistant professor of Neurology, and Shen a professor of Neurology at Harvard Medical School. Additional co-authors of the Neuron paper are lead author Dan Xia, PhD, a research fellow affiliated with both the BWH and MGH Departments of Neurology; Hirotaka Watanabe, PhD, Bei Wu, and Sang Hun Lee, BWH Center for Neurologic Diseases; and Yan Li, PhD, Evgeny Tsvetkov, and Vadim Bolshakov, PhD, McLean Hospital. The study was supported by grants NS041783, NS042818 and NS075346, from the National Institute for Neurological Disorders and Stroke, part of the National Institutes of Health; the Alzheimer’s Association, and the Pew Scholars Program in the Biomedical Sciences.
Researchers at the University of California, San Diego School of Medicine have identified a gene variant that may be used to predict people most likely to respond to an investigational therapy under development for Alzheimer’s disease (AD). The study, published March 12 in *Cell Stem Cell*, is based on experiments with cultured neurons derived from adult stem cells.

“Our results suggest that certain gene variants allow us to reduce the amount of beta amyloid produced by neurons,” said senior author Lawrence Goldstein, PhD, director of UC San Diego Sanford Stem Cell Clinical Center and UC San Diego Stem Cell Program. “This is potentially significant for slowing the progression of Alzheimer’s disease.” AD is the most common cause of dementia in the United States, afflicting one in nine people age 65 and older.

The genetic risk factor investigated are variants of the SORL1 gene. The gene codes for a protein that affects the processing and subsequent accumulation of beta amyloid peptides, small bits of sticky protein that build up in the spaces between neurons. These plaques are linked to neuronal death and related dementia.

Previous studies have shown that certain variants of the SORL1 gene confer some protection from AD, while other variants are associated with about a 30 percent higher likelihood of developing the disease. Approximately one-third of the U.S. adult population is believed to carry the non-protective gene variants.

The study’s primary finding is that variants in the SORL1 gene may also be associated with how neurons respond to a natural compound in the brain that normally acts to protect nerve cell health. The protective compound, called BDNF, short for brain-derived neurotrophic factor, is currently being investigated as a potential therapy for a number of neurological diseases, including AD, because of its role in promoting neuronal survival.
Larry Goldstein, Ph.D.

For the study, UC San Diego researchers took skin cells from 13 people, seven of whom had AD and six of whom were healthy control subjects, and reprogrammed the skin cells into stem cells. These stem cells were coaxed to differentiate into neurons, and the neurons were cultured and then treated with BDNF.

The experiments revealed that neurons that carried disease-protective SORL1 variants responded to the therapy by reducing their baseline rate of beta amyloid peptide production by, on average, 20 percent. In contrast, the neurons carrying the risk variants of the gene, showed no change in baseline beta amyloid production.

“BDNF is found in everyone’s brain,” said first author Jessica Young, PhD, a postdoctoral fellow in the Goldstein laboratory. “What we found is that if you add more BDNF to neurons that carry a genetic risk factor for the disease, the neurons don’t respond. Those with the protective genetic profile do.”

“The value of this kind of stem cell study is that it lets us probe the uniquely human aspects of disease and identify how a person’s DNA might determine their drug response, in this case to a potential treatment for Alzheimer’s,” Young said. “Future clinical trials on BDNF should consider stratifying patients based on their SORL1 risk factor and likelihood of benefiting from the therapy.”

Co-authors include Jonathan Boulanger-Weill, Daniel A. Williams, Grace Woodruff, Floyd Buen, Arra C. Revilla, Cheryl Herrera, Mason A. Israel, Shauna H. Yuan, and Steven D. Edland, all at UC San Diego.

Funding for the study was provided, in part, by the California Institute of Regenerative Medicine, A.P. Giannini Foundation for Medical Research, BrightFocus Foundation and the National Institutes of Health (grant 2P50AG005131-31).
Add Nature, Art and Religion to Life’s Best Anti-Inflammatories

By Yasmin Anwar, UC Berkeley

Taking in such spine-tingling wonders as the Grand Canyon, Sistine Chapel ceiling or Schubert’s “Ave Maria” may give a boost to the body’s defense system, according to new research from UC Berkeley.

Researchers have linked positive emotions – especially the awe we feel when touched by the beauty of nature, art and spirituality – with lower levels of pro-inflammatory cytokines, which are proteins that signal the immune system to work harder.

“Our findings demonstrate that positive emotions are associated with the markers of good health,” said Jennifer Stellar, a postdoctoral researcher at the University of Toronto and lead author of the study, which she conducted while at UC Berkeley.

While cytokines are necessary for herding cells to the body’s battlefields to fight infection, disease and trauma, sustained high levels of cytokines are associated with poorer health and such disorders as type-2 diabetes, heart disease, arthritis and even Alzheimer’s disease and clinical depression.

It has long been established that a healthy diet and lots of sleep and exercise bolster the body’s defenses against physical and mental illnesses. But the Berkeley study, whose findings were just published in the journal Emotion, is one of the first to look at the role of positive emotions in that arsenal.

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“That awe, wonder and beauty promote healthier levels of cytokines suggests that the things we do to experience these emotions – a walk in nature, losing oneself in music, beholding art – has a direct influence upon health and life expectancy,” said UC Berkeley psychologist Dacher Keltner, a co-author of the study.

In two separate experiments, more than 200 young adults reported on a given day the extent to which they had experienced such positive emotions as amusement, awe, compassion, contentment, joy, love and pride. Samples of gum and cheek tissue, known as oral mucosal transudate, taken that same day showed that those who experienced more of these positive emotions, especially awe, wonder and amazement, had the lowest levels of the cytokine, Interleukin 6, a marker of inflammation.

In addition to autoimmune diseases, elevated cytokines have been tied to depression. One recent study found that depressed patients had higher levels of the pro-inflammatory cytokine known as TNF-alpha than their non-depressed counterparts. It is believed that by signaling the brain to produce inflammatory molecules, cytokines can block key hormones and neurotransmitters – such as serotonin and dopamine – that control moods, appetite, sleep and memory.

In answer to why awe would be a potent predictor of reduced pro-inflammatory cytokines, this latest study posits that “awe is associated with curiosity and a desire to explore, suggesting antithetical behavioral responses to those found during inflammation, where individuals typically withdraw from others in their environment,” Stellar said.

As for which came first – the low cytokines or the positive feelings – Stellar said she can’t say for sure: “It is possible that having lower cytokines makes people feel more positive emotions, or that the relationship is bidirectional,” Stellar said.

In addition to Stellar and Keltner, other co-authors and researchers on the study are Neha John-Henderson at the University of Pittsburgh and Craig Anderson, Amie Gordon and Galen McNeil at UC Berkeley.
For information on the following studies please visit:

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

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

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

The CONNECT Study is Testing Whether an Experimental Drug, AZD0530 (saracatinib), Will Slow Progression in Mild-Stage Alzheimer’s Disease.
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SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

More studies coming later in 2015.....