Researchers have uncovered a unique connection between diabetes and Alzheimer’s disease, providing further evidence that a disease that robs people of their memories may be affected by elevated blood sugar, according to scientists at Washington University School of Medicine in St. Louis.

While many earlier studies have pointed to diabetes as a possible contributor to Alzheimer’s, the new study – in mice – shows that elevated glucose in the blood can rapidly increase levels of amyloid beta, a key component of brain plaques in Alzheimer’s patients. The buildup of plaques is thought to be an early driver of the complex set of changes that Alzheimer’s causes in the brain.

The research is published May 4 in The Journal of Clinical Investigation.

“Our results suggest that diabetes, or other conditions that make it hard to control blood sugar levels, can have harmful effects on brain function and exacerbate neurological conditions such as Alzheimer’s disease,” said lead author Shannon Macauley, PhD, a postdoctoral research scholar. “The link we’ve discovered could lead us to future treatment targets that reduce these effects.”

People with diabetes can’t control the levels of glucose in their blood, which can spike after meals. Instead, many patients rely on insulin or other medications to keep blood sugar levels in check.

To understand how elevated blood sugar might affect Alzheimer’s disease risk, the researchers infused glucose into the bloodstreams of mice bred to develop an Alzheimer’s-like condition.

In young mice without amyloid plaques in their brains, doubling glucose levels in the blood increased amyloid beta levels in the brain by 20 percent.
Shannon Macauley, PhD, and David Holtzman, MD, neurology researchers at Washington University School of Medicine in St. Louis, have found a new link between Alzheimer’s disease and diabetes. Their research, in mice, suggests elevated blood sugar can harm brain function.

When the scientists repeated the experiment in older mice that already had developed brain plaques, amyloid beta levels rose by 40 percent.

Looking more closely, the researchers showed that spikes in blood glucose increased the activity of neurons in the brain, which promoted production of amyloid beta. One way the firing of such neurons is influenced is through openings called KATP channels on the surface of brain cells. In the brain, elevated glucose causes these channels to close, which excites the brain cells, making them more likely to fire.

Normal firing is how a brain cell encodes and transmits information. But excessive firing in particular parts of the brain can increase amyloid beta production, which ultimately can lead to more amyloid plaques and foster the development of Alzheimer’s disease.

To show that KATP channels are responsible for the changes in amyloid beta in the brain when blood sugar is elevated, the scientists gave the mice diazoxide, a glucose-elevating drug commonly used to treat low blood sugar. To bypass the blood-brain barrier, the drug was injected directly into the brain.

The drug forced the KATP channels to stay open even as glucose levels rose. Production of amyloid beta remained constant, contrary to what the researchers typically observed during a spike in blood sugar, providing evidence that the KATP channels directly link glucose, neuronal activity and amyloid beta levels.

Macauley and her colleagues in the laboratory of David M. Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology, are using diabetes drugs in mice with conditions similar to Alzheimer’s to further explore this connection.

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Diabetes and AD cont’d…..

“Given that KATP channels are the way by which the pancreas secretes insulin in response to high blood sugar levels, it is interesting that we see a link between the activity of these channels in the brain and amyloid beta production,” Macauley said. “This observation opens up a new avenue of exploration for how Alzheimer’s disease develops in the brain as well as offers a new therapeutic target for the treatment of this devastating neurologic disorder.”

The researchers also are investigating how changes caused by increased glucose levels affect the ability of brain regions to network with each other and complete cognitive tasks.

The research was supported by the National Institutes of Health (NIH), grants F32 NS080320, P01 NS080675; the National Science Foundation (NSF), grant DGE-1143954; and the JPB Foundation.

Imaging Dementia—Evidence for Amyloid

By Michael Rafii, M.D., PhD
UC San Diego

In a truly exciting development, the Centers for Medicare & Medicaid Services (CMS) has approved a four-year, $100 million study called Imaging Dementia—Evidence for Amyloid Scanning 'IDEAS'. The goal of the study is to better understand whether getting an amyloid PET scan can affect the diagnosis, management, and care of individuals whose cognitive symptoms cannot be diagnosed with current techniques. There will be approximately 18,500 patients enrolled from over 200 imaging centers around the country. CMS will reimburse for one amyloid scan for each cognitively impaired person taking part in a clinical trial, if that trial collects data about how the scan subsequently affected the patient’s health outcomes. As readers of this blog will recall, amyloid PET scans, though FDA approved, are not currently covered by any insurance.

The participants in the IDEAS study will be Medicare beneficiaries aged 65 and older. Before a patient gets a scan, the clinician will complete a case report form with the diagnosis and treatment plan. Patients will then undergo amyloid PET imaging and three months after the referral, the clinician will submit a second, updated report that details any change in diagnosis and/or treatment plan resulting from the amyloid PET scan. Participants will learn the results of the amyloid scan.

Perhaps the greatest impact of the IDEAS study will be on patients with the syndrome called Mild Cognitive Impairment (MCI), which presents with symptoms of memory loss and can result from multiple causes, including AD, about half of the time. In a patient with MCI, where the amyloid scan is negative, a diagnosis of AD is essentially ruled out. This type of information will help clinicians tailor diagnostic work-ups and treatment plans more clearly with a better sense of the patient’s amyloid status in hand.
$10 Million in New Funding Adds Innovative Dimensions to Alzheimer’s Disease Prevention Trial

Courtesy of the Alzheimer’s Association

CHICAGO, May 29, 2015 – The Alzheimer’s Association, GHR Foundation and Fidelity Biosciences Research Initiative today announced $10 million in new research funding to Banner Alzheimer’s Institute (BAI), Phoenix, Arizona, to support a groundbreaking Alzheimer’s disease prevention trial that will launch later this year.

The funding, to be paid over five years as part of a broad public/private partnership, supports and extends the Alzheimer’s Prevention Initiative (API) APOE4 trial. The study is focused on determining whether therapies targeting amyloid proteins in the brain may prevent or delay the emergence of Alzheimer's symptoms in people at particularly high genetic risk for developing the disease at older ages.

The new funding will support three aspects of the API APOE4 trial that otherwise would not be possible: (1) brain PET imaging at the start of the trial and two-year follow-up in 125 participants each year, (2) a sub-study to evaluate two remote genetic counseling approaches, and (3) expansion of the Alzheimer’s Prevention Registry for the APOE4 trial.

“The goal is to accelerate the global effort to eliminate Alzheimer’s disease,” said Maria Carrillo, Ph.D., Alzheimer's Association Chief Science Officer. “Through efforts such as API, the Alzheimer’s Association envisions a time when we will have effective treatments to slow or stop Alzheimer's in its tracks; plus preventive strategies and gold-standard care for all people affected by Alzheimer's.”

The Alzheimer's Association led the effort to bring the three funding organizations together. The award to API includes a $5 million lead gift from the GHR Foundation, a private family foundation.

API is led by BAI’s executive director, Eric Reiman, M.D., its director, Pierre Tariot, M.D., and one of its principal scientists, Jessica Langbaum, Ph.D.

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“We are extremely grateful to these three organizations for their extraordinary support,” said Dr. Reiman. “These funds will not only help make it possible to evaluate two promising Alzheimer’s prevention therapies, but to do so in a way that will help the field find treatments that work as soon as possible.”

API was established to rapidly evaluate potential new treatments in people prior to developing clinical symptoms of Alzheimer’s who, based on their age and genetic background, are at highest risk of developing symptoms of the disease, including the API APOE4 trial and the Autosomal Dominant Alzheimer’s Disease Trial. That study is evaluating an investigational anti-amyloid therapy in 300 cognitively normal members of an extended family in Colombia, South America that includes carriers of a rare genetic mutation causing them to develop Alzheimer’s by about age 45. API is committed to sharing trial data and biological samples with the research community to help find better ways to test prevention therapies in the future, and to clarifying the role of APOE genetic testing and disclosure.

The API APOE4 trial is focused on how two investigational anti-amyloid therapies may prevent or delay the development of Alzheimer’s symptoms in a population known to be at high risk for the disease because of their age and genetic status. Specifically, participants in the trial must be age 60-75 and carry two copies of the APOE-e4 gene that greatly increases their risk for developing Alzheimer’s.

The trial will test two different potential therapies to see if one or both can prevent the development of memory and thinking symptoms of Alzheimer’s. The first treatment is an active immunotherapy aimed at triggering the body’s immune system to produce antibodies that block different forms of the amyloid protein, which many researchers believe plays a critical role in the development of Alzheimer’s. The second drug is designed to prevent the production of amyloid protein that accumulates in the brain to form plaques, one of the hallmarks of Alzheimer’s. The trial will involve about 1,300 research participants. Pending regulatory approval, the study is planned to begin in the late 2015/early 2016 in sites in North America and Europe, and last five years.

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The new funding will support three aspects of the API APOE4 trial:

 Tau PET imaging, amyloid PET imaging, and FDG-PET imaging at baseline and two year follow-up in 125 participants each year to determine if the two treatments change tau PET measurements and are associated with a therapeutic benefit. Tau protein helps maintain normal cell structure. In people with Alzheimer’s, tau in the brain becomes abnormal and forms tangles, one of the characteristic features of Alzheimer’s.

 The expansion of the Alzheimer’s Prevention Registry, which provides information about Alzheimer’s prevention research and is intended to support enrollment in the APOE4 trial and other prevention trials. Evaluation of two remote genetic counseling approaches using telephone versus real-time videoconference counseling. This will include measuring the psychological, behavioral and cognitive effects of APOE genotype disclosure in people who underwent both types of genetic counseling.

 “Because participation in the API APOE4 trial requires knowledge of one’s genetic status, we need to determine how to best communicate the genetic risk for developing Alzheimer’s as well as how to counsel individuals on what this risk means,” said Dr. Tariot.

 In September 2013, the U.S. National Institutes of Health (NIH) announced an initial commitment of $33.2 million in partial support for the API APOE4 trial. In July 2014, BAI announced a partnership with Novartis, which is providing its two investigational treatments and financial support. In its NIH grant applications, BAI committed to obtaining $15 million in philanthropic and in kind contributions. To support the API APOE4 trial, $5 million has been obtained through donations to the Banner Alzheimer’s Foundation. The $10 million award from the Alzheimer’s Association, GHR Foundation and Fidelity Biosciences Research Initiative completes Banner’s commitment for this trial.

 Alzheimer’s Prevention Initiative -- The Alzheimer’s Prevention Initiative (API) is an international collaborative formed to launch a new era of Alzheimer’s prevention research. Led by the Banner Alzheimer’s Institute, API conducts prevention trials in cognitively healthy people at increased genetic risk for Alzheimer’s disease. It will continue to establish the brain imaging, biological and cognitive measurements needed to rapidly test promising prevention therapies and has created the Alzheimer’s Prevention Registry to support enrollment in future prevention trials. For more information, go to www.endALZnow.org.
Researchers Clarify Role of Genetic Risk Factor in Alzheimer’s

The study sheds light on potential therapeutic targets for treatment of the disease

By Les Dunseith for University of Southern California News

Snapshot of a neurovascular unit, consisting of neurons (pink), astrocytes (blue), resident microglia (green), a penetrating arteriole and capillaries (white) (Photo/Zlokovic Lab)

Scientists at the Keck School of Medicine of USC have discovered that a protein known as PICALM regulates removal of toxic plaques from the brain, which could be a potential therapeutic target for the treatment of Alzheimer’s disease.

In a study that appeared in a recent edition of *Nature Neuroscience*, researchers identify this new role for PICALM, which is a known genetic risk factor for Alzheimer’s disease.

Alzheimer’s is the most common type of dementia, characterized by the loss of memory and other mental abilities linked to an accumulation of amyloid-beta and other toxic compounds in the brain.

The study found that a deficiency in PICALM in cerebral blood vessels and in PICALM-related gene variants associated with increased risk for Alzheimer’s, disable amyloid-beta from being cleared out of the brain across a region known as the blood-brain barrier.

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“There have been many new genes discovered to be associated with Alzheimer’s disease, but the biology of these genes are poorly understood,” said the study’s principal investigator Berislav Zlokovic, director of the Zilkha Neurogenetic Institute and holder of the Mary Hayley and Selim Zilkha chair for Alzheimer’s Disease research at the Keck School of Medicine. “Our new study shows that a deficiency in PICALM in blood vessels and its variants associated with increased risk for the disease inactivate amyloid-beta clearance from the brain, leading to its accumulation and cognitive impairment. This new study provides fundamental new information about PICALM and brings to light novel potential therapeutic targets for increasing amyloid-beta clearance in Alzheimer’s disease.”

For more than two decades, Zlokovic and his research team have studied the cellular and molecular mechanisms of brain blood vessels that maintain normal cognition with hopes of developing new treatments for Alzheimer’s and other neurodegenerative diseases. One focus of their lab at the Zilkha Neurogenetic Institute is on PICALM, or phosphatidylinositol binding clathrin assembly protein, which in humans is encoded by the PICALM gene.

By performing a neuropathological study in humans with Alzheimer’s and using transgenic animals to model the disease, the group found that low levels of PICALM in brain endothelial cells lead to amyloid-beta accumulation in the brain. Genetic variants associated with the PICALM gene have been shown to increase the risk of Alzheimer’s disease.

The researchers also generated human endothelial cells from induced pluripotent stem cells to examine the consequences of a known PICALM variant associated with increased risk for Alzheimer’s; they found that this genetic alteration disrupted amyloid-beta clearance by cerebral blood vessels.

These new findings have prompted Zlokovic to address new questions about the role of PICALM in Alzheimer’s. Future studies will explore how genetic flaws in the PICALM gene influence its expression levels and clearance function at the blood-brain barrier and the general health of cerebral blood vessels. The team also will work on developing therapeutic strategies, including gene therapy, and screening for new drugs to overcome PICALM deficiency.

USC co-authors on the study include Zhen Zhao, Abhay Sagare, Qingyi Ma, Matthew Halliday, Pan Kong, Kassandra Kisler, Ethan Winkler, Anita Ramanathan, Nelly Chuqui Owens, Sanket Rege, Gabriel Si, Ashim Ahuja, Carol Miller, Tohru Sugawara and Justin Ichida.

The study was funded in part by the National Institutes of Health (R37NS34467, R37AG23084, R01AG039452, R01AG035355, R01AG027924, R00NS07743), Cure for Alzheimer Fund, American Cancer Society (RSG–13–379–01–LIB), Rainwater Charitable Foundation, Donald E. and Delia B. Baxter Foundation, and Daiichi Sankyo Foundation of Life Science. The study used sample ND10689 from the National Institute of Neurological Disorders and Stroke Cell Line Repository as well as clinical data.
ADCS Clinical Trials Enrolling...

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 Study for People with Mild to Moderate Alzheimer’s Disease

The CONNECT Study for people with Mild-Stage Alzheimer’s Disease.
On a temporary enrollment hold until further notice:

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

More studies coming later in 2015.....