Fruit Flies Yield Insights into Aging

Both calorie restriction and resveratrol—a compound found in grapes, red wine, and nuts—ward off several age-related diseases in animal models. Researchers have been exploring the molecular mechanisms involved. Recent studies have implicated an enzyme called AMP-activated protein kinase (AMPK). AMPK senses and maintains energy levels in the cell. Among its many effects, it helps to regulate autophagy, a recycling process that continually breaks down and recycles waste within our cells. Autophagy has also been linked to aging and lifespan.

A team led by Dr. David Walker at the University of California, Los Angeles, used transgenic technology to manipulate AMPK levels in specific organs of fruit flies (Drosophila) and explored the impact on autophagy, cellular signs of aging, and lifespan. The study was funded by NIH’s National Institute on Aging (NIA) and National Institute of General Medical Sciences (NIGMS). Results appeared online in Cell Reports on September 3, 2014.

The researchers found that boosting AMPK levels in the nervous system (neurons) induced autophagy within the brain and prolonged the flies’ lifespan. Surprisingly, boosting neuronal AMPK also induced autophagy in the flies’ intestines and improved a measure of intestinal aging. It induced autophagy and reduced signs of aging in muscle as well.

Autophagy can be directly induced in Drosophila by increasing expression of the gene Atg1. When the researchers raised expression of Atg1 in adult fly neurons, it also improved intestinal function during aging and prolonged lifespan. Further experiments showed that the anti-aging effects of neuronal AMPK disappeared when Atg1 was blocked.

The team next raised levels of AMPK in the intestine. This similarly boosted autophagy, both in the intestine and the brain. It also reduced signs of aging in muscle tissue and prolonged life. To investigate how AMPK and Atg1 might exert these system-wide effects, the researchers explored the insulin/insulin-growth-factor-1-signaling pathway, which had previously been linked to lifespan in flies and mammals. Their results suggest that AMPK and Atg1 affect other tissues by altering insulin-like peptide signaling.

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“We have shown that when we activate the [AMPK] gene in the intestine or the nervous system, we see the aging process is slowed beyond the organ system in which the gene is activated,” Walker says.

Autophagy may slow the aging process by increasing the turnover of damaged cell components. Which of these components might be relevant to aging remains to be discovered. Researchers will also need to test whether activation of autophagy in a single tissue in mammals can slow aging in other tissues as well.

—by Harrison Wein, Ph.D., National Institutes of Health

Overcompensation — It Could Work for the Brain

Some people seem to cope better than others with having amyloid plaques in their brains. According to a study in the September 14 Nature Neuroscience, they maintain cognitive prowess by kicking neural networks into overdrive. Such hyperactivity had been observed before, but researchers were unsure if it was beneficial. The new study, led by William Jagust at the University of California, Berkeley, suggests that it is. In cognitively normal people harboring amyloid, those with greater activation remembered in greater detail.

“This is incredibly intriguing,” said John Cirrito of Washington University, who was not involved in the study. “One of the most remarkable things about the brain is that it adapts and compensates in response to injury.”

Cognitively normal people whose brains are riddled with amyloid plaques have baffled AD researchers, especially those who subscribe to the hypothesis that amyloid causes the disease. Some neural networks are hyperactive when otherwise healthy people with brain Aβ perform learning and memory tasks, while other networks fail to switch off when they should. Researchers have wondered whether these abnormal neural activation patterns reflect a dedicated compensatory mechanism, a harbinger of dementia, or both.

As a memory is made, the brain tones down activity in some regions (blue), while ramping it up in others (orange). People who have amyloid in their brain seem to compensate for it by activating those brain regions even more. [Image courtesy of Elman et al., Nature Neuroscience 2014.]

To address the first possibility, co-first authors Jeremy Elman and Hwamee Oh tested whether rises in neural activity in people harboring amyloid plaques correlated with better memory. They studied 22 healthy young participants and 49 cognitively normal people over age 65. The researchers split the older participants into two groups—amyloid positive and amyloid negative—based on PiB retention. All were presented with a series of complex images of everyday scenes, while their neural activity was recorded via fMRI. Fifteen minutes later, the researchers showed the participants a simple true-or-false question about each of the images to assess the extent of their “gist memory.” If a person remembered the gist of the image, for example, whether it showed a boy on a skateboard, then the researchers asked six more detailed questions about the image to measure the richness of the memory, e.g., was he wearing a blue shirt? On average, the three groups performed equally well on the memory tests. The researchers then averaged the participants’ memory scores and correlated them with the patterns of neural activity observed while the memories were encoded.
Overall, the investigators found that when people were viewing a picture they later remembered, the regions of the brain involved in memory—called the task-positive network, or TPN—lit up, whereas the default mode network (DMN), which normally fires while the brain is at rest, was shut down (see image above). Compared with older people without amyloid, people with amyloid displayed higher levels of neural activity in the TPN and lower levels of DMN deactivation when looking at images that they later recalled.

The researchers took advantage of the memory detail data to determine whether heightened neural activity in people with amyloid deposition gave them an edge. They correlated the number of details each participant recalled with their neural activity when the memory was made. For older people devoid of amyloid, neural activity in the TPN switched on, but did not ramp up linearly with more details being recalled. Rather, the DMN progressively deactivated as the details improved in this group. In contrast, in both young people and older people with amyloid, TPN activation, but not deactivation of the DMN, correlated with greater details remembered.

“People with amyloid recalled more details as their brain activity went up, so that seems to tell us that this ramping up of activity serves a function,” Jagust told Alzforum. “It’s not some kind of random noise, and in fact it seems to be helping people,” he said. Older people without amyloid may rely more on the deactivation of the DMN to focus, as opposed to the increases of TPN activity seen in people with amyloid, he speculated.

Gael Chetelat of the French Institute of Health and Medical Research in Paris agreed that this was one possible explanation. “While in normal aging, difficulties may arise from an inability to focus attention resources on the task, elderly with amyloid deposits specifically increase their activity in task-related regions to maintain their performance,” she wrote in an email to Alzforum.

Interestingly, in people with the highest levels of amyloid, the researchers noticed that the tight coupling between neural activity and detailed recall started to unravel. “This might be a sign that this compensation wears out,” Jagust suggested, although the researchers will not know this until follow-up studies are done.

Previous studies have reported that neuronal activity triggers the release of amyloid and tau. This suggests that this compensatory mechanism, though beneficial in the short run, could one day lead to a further spread of pathology, said Willem Huijbers of Harvard University. “Something might be beneficial for memory performance, but in the long run it could be detrimental to the brain,” he said, “That’s the question you’re left with.”

—Jessica Shugart

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Normal Brain Function Without Any Form of ApoE

ApoE is a protein that binds to and transports cholesterol throughout the body, including the brain. Since 1993, researchers in the Alzheimer’s field have known that one form of ApoE, called ApoE4 significantly increases the risk for developing AD and brings the disease on at an earlier age. People with one copy of ApoE4 are eight times more likely to develop AD, and those with two copies of ApoE4 are about 12 times more likely. About 20 percent of the general population has at least one copy of ApoE4.

The ApoE protein actually exists in three major forms (ApoE2, E3, E4) and the risk for getting AD differs with each form, E4>E3>E2. ApoE4 is thought to bind directly to beta-amyloid, forming a complex molecule. Work published a few years ago showed that the binding of ApoE4 to beta-amyloid shifts the removal of beta-amyloid out of the brain from a rapid export pathway, to a very slow pathway, resulting in poor beta-amyloid clearance from the brain, and hence, its accumulation within the brain. Furthermore, researchers showed that not only does ApoE4 lead to accumulation of beta-amyloid in the brain, but it also seems to be specifically routing beta-amyloid to synapses, connections between neurons, where it leads to additional injury. Other mechanisms exist in the brain to also remove beta-amyloid and are independent of this ApoE mechanism. Because of this, some treatments being developed for AD target ApoE and aim to alter its function.

Last month, researchers at UC San Francisco reported on a 40 year old patient whose body produces no ApoE protein whatsoever. The condition, called dysbetalipoproteinemia is characterized by high blood levels of cholesterol as a consequence of poor clearance from the blood. The researchers conducted extensive neurological tests and found his cognition to be essentially normal. They performed MRI scans of the patient’s brain which revealed normal brain size, with no signs of the atrophy, or shrinkage in the hippocampus, a key finding that characterizes AD. They also measured levels of AD-related proteins such as beta-amyloid and Tau in his cerebrospinal fluid, which were also normal.

What do these results mean? Perhaps the most important take away message is that one can have normal brain function without any form of ApoE protein. Certainly other mechanisms are at work removing beta-amyloid out of the brain, and ApoE is just one component. But the notion that completely blocking ApoE, particularly in patients with ApoE4, to reduce the risk of AD may be worth examining further.

By Michael Rafii, MD, PhD
Medical Core Director
Alzheimer’s Disease Cooperative Study
University of California San Diego
Mayo Researchers Reveal Pathway that Contributes to Alzheimer’s Disease

JACKSONVILLE, Fla. — Researchers at Jacksonville’s campus of Mayo Clinic have discovered a defect in a key cell-signaling pathway they say contributes to both overproduction of toxic protein in the brains of Alzheimer’s disease patients as well as loss of communication between neurons — both significant contributors to this type of dementia. Their study, in the online issue of Neuron, offers the potential that targeting this specific defect with drugs “may rejuvenate or rescue this pathway,” says the study’s lead investigator, Guojun Bu, Ph.D., a neuroscientist at Mayo Clinic, Jacksonville, Fla.

“This defect is likely not the sole contributor to development of Alzheimer’s disease, but our findings suggest it is very important, and could be therapeutically targeted to possibly prevent Alzheimer’s or treat early disease,” he says.

The pathway, Wnt signaling, is known to play a critical role in cell survival, embryonic development and synaptic activity — the electrical and chemical signals necessary for learning and memory. Any imbalance in this pathway (too much or too little activity) leads to disease — the overgrowth of cells in cancer is one example of overactivation of this pathway. While much research on Wnt has focused on diseases involved in overactive Wnt signaling, Dr. Bu’s team is one of the first to demonstrate the link between suppressed Wnt signaling and Alzheimer’s disease.

“Our finding makes sense, because researchers have long known that patients with cancer are at reduced risk of developing Alzheimer’s disease, and vice versa,” Dr. Bu says. “What wasn’t known is that Wnt signaling was involved in that dichotomy.”

Using a new mouse model, the investigators discovered the key defect that leads to suppressed Wnt signaling in Alzheimer’s. They found that the low-density lipoprotein receptor-related protein 6 (LRP6) is deficient, and that LRP6 regulates both production of amyloid beta, the protein that builds up in the brains of AD patients, and communication between neurons. That means lower than normal levels of LRP6 leads to a toxic buildup of amyloid and impairs the ability of neurons to talk to each other.

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Defective Wnt signaling resulting from loss of LRP6 causes dendritic spines and synapses to degenerate, thereby impairing communications among neurons in the brain.

Mice without LRP6 had impaired Wnt signaling, cognitive impairment, neuroinflammation and excess amyloid.

The researchers validated their findings by examining postmortem brain tissue from Alzheimer’s patients — they found that LRP6 levels were deficient and Wnt signaling was severely compromised in the human brain they examined.

The good news is that specific inhibitors of this pathway are already being tested for cancer treatment. “Of course, we don’t want to inhibit Wnt in people with Alzheimer’s or at risk for the disease, but it may be possible to use the science invested in inhibiting Wnt to figure out how to boost activity in the pathway,” Dr. Bu says.

“Identifying small molecule compounds to restore LRP6 and the Wnt pathway, without inducing side effects, may help prevent or treat Alzheimer’s disease,” he says. “This is a really exciting new strategy — a new and fresh approach.”

Researchers from the University of Kentucky, Xiamen University in China, the University of Oklahoma and the Korea Brain Research Institute participated in the study. This research was primarily supported by research grants from the National Institutes of Health (R01AG027924, R01AG035355, R01AG046205, P01AG030128, and P01NS074969), Alzheimer's Association and the Mayo Clinic Center for Regenerative Medicine Career Development Award.

— Kevin Punsky, Mayo Clinic
Stress and its Influence on Alzheimer’s Disease

Aging is an inevitable journey for everyone, and includes many obstacles and different paths to take. How we live our lives can have enormous impact on whether we grow old gracefully, or succumb along the way. Good physical health, through diet and exercise, will allow people to remain active well into their twilight years, but as lifespan increases it is also important to take care of and maintain brain health as well. Fortunately, it appears that what is good for the heart is also good for the brain, and thus by keeping active, both physically and mentally, and maintaining a healthy diet rich in omega 3 fatty acids, a person can have the best chance of aging successfully, and avoid both heart disease and brain disease.

The major brain disease of the elderly is Alzheimer's disease. It affects 1 in 20 people aged 65 and over, and its incidence increases with age such that around half of people aged 85 and over have the disease. Alzheimer’s disease is a devastating disorder that robs a person of their memories and cognitive abilities, rendering them unable to recognize family members, or care for themselves. But what is it that causes Alzheimer’s disease? Why do some people develop Alzheimer’s disease and not others? By asking, and then understanding these questions, we, as scientists, can develop therapies and strategies to help people avoid developing the disease in old age.

Here within UCI MIND, we have devoted considerable resources to identifying the causes of Alzheimer’s disease, and finding ways to circumvent these causes. We have identified how the stress hormone cortisol can play a role in the development of Alzheimer’s disease. Cortisol is a steroid hormone that is produced in the adrenal gland in response to times of stress. In the short term, following a stressful experience, cortisol levels rapidly increase in the bloodstream, and its presence is helpful – improving short-term memory formation and adapting the body’s physiology to deal with the situation effectively. However, long-term stress leads to prolonged elevated levels of cortisol within the bloodstream, which can have serious deleterious effects.

It was found, over twenty years ago, that patients with Alzheimer’s disease had elevated levels of cortisol in their blood streams, compared to healthy patients. This elevation correlated with the degree of memory impairments that the patients had and appeared early on in the disease progression. We were interested in whether or not these early increases in circulating cortisol could be contributing to the development of Alzheimer’s disease, by leading to the pathologies that are found in the AD brain. It is the accumulation of sticky proteins in the brain, leading to a loss of neuronal function, which underlies the dementia and memory loss seen in Alzheimer’s disease. Typically 2 sticky proteins are present in the Alzheimer’s disease brain – the first is the amyloid-beta peptide (Ab), which stick together inbetween neurons and form the extracellular plaques.

The second sticky protein is known as tau, which becomes modified in the Alzheimer’s disease brain causing it to stick together inside neurons and disrupting normal neuronal function. The net result of these sticky proteins is a cascade of events leading to widespread synaptic and neuronal loss in the brain, which causes the dementia and memory loss.

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We showed that cells treated with cortisol produced dramatically larger amounts of this Ab peptide – which can accumulate to form the Ab plaques. In order to test whether increased cortisol could have a similar effect in animals and by extension people we turned to a genetically altered mouse, which had been engineered to develop Alzheimer’s disease pathology in its brain as it aged. We took young animals, before they were old enough to have Alzheimer’s disease pathology, and we injected them with a rodent equivalent of cortisol every day for one week. After just a single week we looked inside the brains of these animals and found that levels of both the Ab peptide and tau protein were tremendously elevated. This showed us that increases in circulating cortisol in humans is able to increase the pathology present in the brain – and thus could make people develop Alzheimer’s disease faster.

So how can we use these findings to help people reduce their risk of developing Alzheimer’s disease in old age? Firstly, cortisol levels are increased by stress – a study has also shown that people with stressful lives are around two to three times more likely to develop Alzheimer’s disease than others. So avoiding stress is paramount. In addition, these results can be used by scientists to develop drugs to block either the production of cortisol, or to prevent its effects once it is produced. This could lead to a slowing of the disease if it proves successful.

Stress reduction, combined with a healthy lifestyle and diet will help people age successfully and avoid disease.

*Courtesy of UCI Mind*
World Alzheimer's Report: Preventing Dementia through Lifestyle Changes

With predictions of a coming global avalanche of dementia cases, researchers are turning their attention to prevention strategies. Based on current data, at least four lifestyle factors robustly affect dementia risk, according to the World Alzheimer Report 2014, released September 16 by the umbrella group Alzheimer’s Disease International and Bupa, the largest private health insurance company in the United Kingdom. Researchers led by Martin Prince at King's College London analyzed previous studies that examined the effects of developmental, psychological, lifestyle, and cardiovascular factors on dementia risk. They found that diabetes heightened risk by 50 percent, while smoking increased the odds of Alzheimer’s disease by the same amount. Hypertension in midlife pumped up the risk for vascular dementia by 60 percent, while education lowered dementia risk by about 40 percent. Factors such as depression and obesity also appeared to inflate risk, while physical activity and cognitive stimulation seemed to lower it, but existing data are not strong enough to draw firm conclusions about those factors, the report noted.

The findings belie the report from a 2010 National Institutes of Health State-of-the-Science panel, which concluded that insufficient evidence existed to endorse any health intervention for lowering Alzheimer’s risk (see May 2010 news story; May 2011 news story). The World Alzheimer Report argues that, “There is persuasive evidence that the dementia risk for populations can be modified through reduction in tobacco use and better control and detection for hypertension and diabetes, as well as cardiovascular risk factors.”

The findings add to a growing body of evidence suggesting that improving heart health and maintaining an active lifestyle and sensible diet wards off dementia (see, e.g., Jul 2014 news story; Apr 2014 news story). Researchers attribute recent drops in dementia incidence in developed countries to higher education levels and better cardiovascular care (see May 2013 news story; Jul 2013 news story; and Jul 2014 news story). In 2011, researchers at the University of California, San Francisco, estimated that reducing the prevalence of the risk factors listed above could significantly cut dementia cases worldwide (see Jul 2011 news story). Those researchers recently refined their analysis, concluding that a drop of 10 percent in each risk factor would reduce Alzheimer’s prevalence in 2050 by 8 percent worldwide (see Norton et al., 2014).

Despite all the research on this topic, the public remains largely unaware of the impact of lifestyle factors. In a survey conducted by Bupa, only a quarter of respondents knew that obesity and physical inactivity could increase their odds of developing dementia, and just one in six realized that social activity could protect them. Alzheimer’s Disease International recommends greater public outreach. “Implementing effective public health campaigns may help to reduce the global risk,” director Marc Wortmann, said in a press release.

—Madolyn Bowman Rogers

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ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

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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:
SNIFF – the Study of Nasal Insulin to Fight Forgetfulness
The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.