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New Insights Into the Development and Treatment of Alzheimer's Disease

Findings reveal a role for genetics and circadian rhythms and suggest future treatment options

SAN DIEGO — Research released today reveals new discoveries about the pathology, development, and potential treatments for Alzheimer's disease. New studies in humans and animal models highlight factors that both contribute to and offer protection from the neurological disorder. The findings were presented at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Alzheimer's disease is an age-related neurological disorder characterized by memory loss and dementia. As the number of Americans age 65 and older continues to grow, Alzheimer's disease is affecting an increasing number of people. By 2025, the number of people with the disease in the United States is estimated to reach more than 7 million, presenting both social and economic challenges.

Despite its prevalence, the underlying causes for most cases of Alzheimer's disease are currently unknown, and there is no preventative medicine or treatment.

Today's new findings show that:

- Healthy elderly people with normal or superior memories can still exhibit signs of Alzheimer's in their brains, suggesting they may possess protective mechanisms (Changiz Geula, abstract 284.1, see attached summary).
- Alzheimer's disease may disrupt sleep-wake cycles in both humans and mouse models of the disease before other symptoms arise (Trongha Xuan Phan, abstract 205.06, see attached summary).
- A gene variant may contribute to the accumulation of brain plaques in the early stages of Alzheimer's disease (Guojun Bu, abstract 225.27, see attached summary).
- A newly developed biomarker may predict response to a regenerative therapy for Alzheimer's disease (Christine Solinsky, abstract 307.03, see attached summary).

"Today's findings represent steps forward in understanding how and why some people develop Alzheimer's disease while others do not," said press conference moderator Roberta Diaz Brinton, PhD, of the University of Southern California. "A better understanding of the contributing factors will help scientists in their efforts to prevent and treat this debilitating disease." Brinton is also an author on one of the presented studies (abstract 307.03).

The research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about Alzehimer's disease at *BrainFacts.org*.

Related Neuroscience 2016 Presentation
Symposia: Microtubule and Tau-Based Therapy for Alzheimer's Disease and Other Brain Disorders
Monday, Nov. 14, 8:30-11 a.m., SDCC 6A

Abstract 284.1 Summary

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Alzheimer's Disease Pathology Can Exist in Brains of Healthy Elderly People

Normal or even cognitively superior elderly people can sometimes exhibit signs of Alzheimer's in their brains

The brains of healthy elderly people with excellent memory performance can also possess pathology characteristic of Alzheimer's disease, according to a study released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. This discovery suggests some elderly people may possess mechanisms that somehow protect against nerve cell death.

The accumulation of abnormal proteins called plaques in the spaces between brain cells and twisted proteins called tangles inside nerve cells are hallmarks of Alzheimer's disease. Both plaques and tangles damage nerve cells, causing cognitive decline, dementia, and cell death.

Recent research shows that plaques and tangles are sometimes found in the brains of cognitively healthy elderly people. In this new study, researchers examined the brains of eight individuals above age 90 who showed superior performance on memory tests. Surprisingly, they found a range of Alzheimer's pathology in these brains, including three brains that qualified as having Alzheimer's disease despite superior memory performance.

The researchers also found that nerve cells in the hippocampus, part of the brain responsible for forming memories, remained relatively intact in elderly people with full Alzheimer's pathology and superior memory performance. However, in the brains of patients with dementia, they found evidence of nerve cell death in this brain region and other brain areas controling cognitive functions.

"These findings point to mechanisms in some elderly that protect their brains against the toxic effects of plaques and tangles normally associated with dementia," said senior author Changiz Geula, PhD, of Northwestern University. "Discovery of these mechanisms is likely to help devise therapies against Alzheimer's disease and may also allow strategies to help normal elderly achieve superior cognitive health."

Research was supported with funds from the National Institute on Aging.

Scientific Presentation: Monday, Nov. 14, 8-8:15 a.m., SDCC 33C

13347, The oldest-old with preserved cognition and the full range of Alzheimer pathology.
A. REZVANIAN[1], D. T. OHM[1], L. KUKREJA[1], T. D. GEFEN[1], S. WEINTRAUB[1], E. ROGALSKI[1], R. KIM[2], C. AGUIRRE[2], M. CORRADA[2], *M.-M. MESULAM[1], C. KAWAS[2], **C. GEULA[1]**;
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TECHNICAL ABSTRACT: Recent reports indicate the presence of amyloid plaques (AP) and neurofibrillary tangles (NFT) in brains of cognitively normal elderly with a density and distribution sufficient for pathologic diagnosis of Alzheimer's disease (AD). The purpose of this study was to investigate whether full AD pathology is present in The 90+ Study participants with preserved cognitive function. Eight 90+ Study participants (95-100 years) were selected based on above average performance on tests of memory and preserved performance in other cognitive domains for their age. The thioflavin-S stain, and antibodies to phosphorylated tau (AT8) and amyloid-β (6E10), were used to assess the presence, density and morphology of AP and NFT. The Cresyl violet Nissl stain and antibodies to non-phosphorylated neurofilaments and microtubule associated protein 2 were employed to assess neuronal density. The hippocampus, parahippocampal gyrus, middle frontal gyrus and inferior parietal cortex were examined. Despite similarly preserved cognitive abilities, the eight cases displayed divergent patterns of AD pathology. One case showed very sparse NFT / Pre-NFT (Braak Stage [BS] I) and diffuse AP. Another showed slightly higher densities of NFT / Pre-NFT (BS II) and a moderate density of diffuse AP. Three cases presented with greater density of NFT / Pre-NFT (BS III) and variable AP density. The remaining three cases were characterized by significantly higher densities and widespread distributions of NFT / Pre-NFT (BS IV, V and VI, respectively), cored / neuritic AP and neuropil threads, with two satisfying criteria for pathologic diagnosis of AD. Apparent density of neurons in the hippocampus and neocortex did not distinguish cases with divergent AD pathology. However, clinically confirmed AD cases, with density and distribution of AP and NFT comparable to 90+ Study brains with the most severe pathology, displayed clear neuronal loss in the hippocampus and neocortex. These results indicate presence of pathologically confirmed AD in the absence of cognitive impairment. It is possible that factors not yet identified mitigate the deleterious effects of AD pathology on neurons, and/or that certain individuals are in fact protected from processes that lead to AP / NFT formation.

Abstract 205.06 Summary

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Biological Clock Disruption May Precede Cognitive Impairment in Alzheimer's Disease

Sleep disruption could potentially play a role in dementia and Alzheimer's disease

Disrupting sleep may accelerate and exacerbate symptoms of Alzheimer's disease in both humans and mice by altering brain cells' abilities to clear out metabolic waste, according to a study released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The 24-hour cycle defining our circadian period dictates when we wake up in the morning and go to sleep at night. Previous research indicates that in its earliest stages, Alzheimer's perturbs patients' sleep. Specifically, research shows disrupted rapid eye movement (REM) sleep precedes cognitive impairment.

In this study, researchers reanalyzed previously published research to examine the molecular basis of circadian rhythm disruption in older adults and determine whether sleep disruption was a symptom of Alzheimer's or a factor in driving the disease. They found the activity of proteins needed to clear out metabolic waste fluctuated in a circadian manner in younger subjects, but it did not in older people, establishing sleep disruption as a potential risk factor for Alzheimer's disease.

The team also examined a mouse model of Alzheimer's disease in which the animals' biological clocks functioned improperly because they lacked a gene critical to the circadian clock. These mice showed memory impairments, weighed less, and had increased numbers of plaques in their brains as compared with control mice. In addition to disrupted sleep patterns, these animals failed to clear metabolic waste normally, just like human Alzheimer's patients.

"This study lends support to the recently developed and interesting hypothesis that circadian rhythm alterations precede dementia and could potentially be one of the causes for dementia and Alzheimer's disease," said lead author Trongha Xuan Phan of Northwestern University.

The researchers are now working on modifying sleep behaviors and increasing REM sleep in the mouse model to see whether this will alleviate plaque formation and restore memory deficits.

Research was supported with funds from Glenn Aging Foundation at MIT.

Scientific Presentation: Sunday, Nov. 13, 2:15-2:30 p.m., SDCC 2

3854, The role of hdac1 in modulating circadian rhythmicity and Alzheimer's disease.
***T. X. PHAN**[1], F. GAO[2], A. NOTT[2], S. GOEL[2], P.-C. PAO[2], S. J. BARKER[2], R. VASSAR[1], L.-H. TSAI[2]; [1]Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [2]Picower Inst. For Learning and Memory, MIT, Cambridge, MA

TECHNICAL ABSTRACT: Histone acetylation is a form of post-translational modification that is dynamically orchestrated by two opposing groups of enzymes: histone acetyl transferases (HATs) and histone deacetylases (HDACs). HATs add an acetyl group while HDACs remove it. HDACs have been demonstrated to play a significant role in developments, cancer biology, DNA repair, memory formation and more. In particular, our lab has shown that HDAC1 gets recruited to DNA double stranded break sites for proper DNA repair. HDAC1 was thus shown to play a protective role against insults that cause DNA damage. In this study, we report that HDAC1 plays an important role in mediating circadian regulation in vivo. Mice with exon 5-7 genetically ablated exhibited period (Tau) deviating from the normal wild type Tau of 23.5 hours, suggesting a novel critical role for HDAC1 in regulating the core molecular clock. In addition, we assessed the sleep architecture in these HDAC1 KO animals by electroencephalogram (EEG). We also assessed their cognitive functions with multiple behavioral assays. Upon further investigation, we observed that HDAC1 binds to the promoter of circadian clock genes Per1 (Period1) and Bmal1 (Brain and Muscle ARNT-Like protein), highlighting the important role of HDAC1 in modulating the expression of core molecular clock proteins. We also have direct evidence supporting the notion that HDAC1 binds to promoters of Alzheimer's disease (AD) risk genes and regulates their expression, implicating a role for HDAC1 in facilitating Abeta clearance. Microdialysis approach was also employed to assess the amount of Abeta throughout circadian cycle to determine whether this pattern of oscillation is altered when we knockout HDAC1. Notably, we did further analysis from previous published work and revealed that the oscillatory expression pattern of AD risk genes in aging healthy (>60 yo) human brain samples were dampened. Collectively, these results reveal the novel and fascinating mechanism by which HDAC1 regulates circadian rhythm and suggest that disruption in circadian rhythm could potentially precede cognitive decline in Alzheimer's disease patients.

Abstract 225.27 Summary

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Gene Variant Linked to Alzheimer's Disease Pathology

Individuals with the APOE4 gene type may be vulnerable to brain plaque development

A genetic variant implicated in Alzheimer's disease risk may drive the earliest stages of disease, according to research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Individuals carrying APOE4, a variant of the apolipoprotein E gene, are more likely to develop Alzheimer's disease than those carrying the neutral APOE3 variant or the protective APOE2 variant. Although only about 20 percent of people carry the APOE4 variant, up to 60 percent of those who develop Alzheimer's disease carry APOE4. Understanding how this gene variant increases the risk of Alzheimer's disease may aid in the development of precision medicine to treat APOE4-positive individuals.

The brains of Alzheimer's disease sufferers are marked by the presence of sticky protein plaques. Increasing evidence indicates the accumulation and aggregation of such plaques initiate a cascade of events ultimately leading to neurodegeneration and dementia. In mouse models, minute amounts of plaque protein can clump together and serve as seeds that then recruit more plaques to form larger clumps at a faster pace. Evidence in humans and animal models show APOE4 increases the accumulation of plaques in the brain; however, it is not known in what stage of the disease APOE4 has the strongest effect.

In this study, researchers developed new mouse models expressing either human APOE3 or APOE4 during different stages of plaque aggregation. They found that the expression of APOE4 during the initial seeding stage is enough to drive plaque development. APOE4 had little effect when present after the initial seeding stage.

"Our findings suggest that therapeutic interventions to treat APOE4-positive individuals need to start early," said senior author Guojun Bu, PhD, of the Mayo Clinic. "With available genetic testing and other methods of risk assessment for Alzheimer's disease, we can focus our efforts to identify high-risk individuals and design prevention or early treatment strategies targeting plaques and other APOE-related pathways."

Research was supported with funds from the National Institute on Aging and Cure Alzheimer's Fund.

Scientific Presentation: Sunday, Nov. 13, 3-4 p.m., Halls B-H

16076, Apolipoprotein E4 drives amyloid pathology in an inducible mouse model – Effects at different stages of amyloid pathology.
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TECHNICAL ABSTRACT: Accumulation of amyloid-β (Aβ) peptide in the brain is a critical and perhaps initiating event in the pathogenesis of Alzheimer's disease (AD). Aβ accumulation leads to the formation of Aβ aggregates which disrupt synaptic functions and may lead to eventual neurodegeneration. Among the three polymorphic alleles, the ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for sporadic AD. In addition to increasing the prevalence of AD, the presence of *APOE4* also lowers the age of onset. Although there is strong evidence from both humans and animal models that apoE4 enhances amyloid pathology, the critical period when apoE4 has the strongest effects on amyloid pathology is not clear. We have developed cell type-specific, inducible mouse models in which the expression of apoE isoforms can be turned on or off in a cell type-specific manner. Using these models, we found that overexpression of apoE4 in astrocytes during the initial seeding stage as oppose to the rapid growth period is critical for its effect on accelerating amyloid and promoting astrogliosis and microgliosis in the background of $APP_{SWE}/PS1_{\Delta E9}$ amyloid model mice. By measuring Aβ half-life using *in vivo*microdialysis, we found that apoE4 inhibits Aβ clearance. Overexpression of apoE3 did not affect the amyloid plaque load or Aβ clearance, but did enhanced synaptic plasticity measured by long-term potentiation. Together, our results define a critical role of apoE4 in driving amyloid pathology during the initial seeding period, likely by inhibiting Aβ clearance and promoting Aβ aggregation. Our findings provide novel mechanistic insights into differential functions of apoE isoforms in amyloid pathogenesis and have implications for designing mechanism-based, apoE-targeted AD therapy.

Abstract 307.03 Summary

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Researchers Develop Biomarker for Nerve Cells' Ability to Regenerate

Study aims to identify Alzheimer's disease drug responders

Currently no drug exists to prevent or treat Alzheimer's disease. Of the more than 100 clinical trials for Alzheimer's medicines, nearly all of them failed. However, if scientists could identify patients most likely to respond to a specific therapeutic, they could potentially improve the success rate of clinical trials of Alzheimer's disease medicines.

That was the goal of researchers who today unveiled the development of a biomarker that may predict and monitor response to Alzheimer's disease therapies. The research was presented at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The researchers are pursuing a regenerative therapy for Alzehimer's that promotes nerve cell self-renewal and repair. They developed a biomarker of regenerative potential using induced pluripotent stem cell (iPSC) technology. By taking blood cells from people with early Alzheimer's disease, the team created individualized neural stem cells that they tested for a response to Allo (allopregnanolone) — a neurosteroid.

In animal models of Alzheimer's disease, Allo enhanced the ability of the brain to regenerate by increasing the number of neural stem cells, boosting energy production in the brain, and reducing the burden of Alzheimer's pathology. The drug also restored the animal's learning and memory to normal. In moving Allo to early-stage clinical testing in people with mild cognitive impairment or early Alzheimer's disease, the researchers studied the function of the cells' energy generators, known as mitochondria, and the regenartive potential of the iPSC-derived neural stem cells from Alzheimer's patients and healthy people. Initial results showed that iPSCs from Alzheimer's patients possessed a distinct pattern of cellular activity compared with healthy people and that Allo improves the mitochondrial function of iPSC-derived neural stem cells.

"Early outcomes indicate that Allo promotes both the regeneration of and energy production within iPSC-derived neural stem cells from people with early Alzheimer's disease," said lead author Christine Solinsky, MPharm, of the University of Southern California in Los Angeles. "Allo treatment restored neural stem cell regeneration and energy production to that of healthy controls. The findings of this study will serve as the foundation for developing the first iPSC-based regenerative biomarker to determine and monitor response to regenerative therapeutics."

Research was supported with funds from the National Institute on Aging, the University of Southern California Provost Fellowship, the California Institute for Regenerative Medicine's Predoctoral Research Traineeship, and the American Foundation for Pharmaceutical Education Fellowship.

Scientific Presentation: Monday, Nov. 14, 10-11 a.m., Halls B-H

8010, Human iPSC-based biomarker strategy to identify neuroregenerative responders to allopregnanolone: proof of concept.
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TECHNICAL ABSTRACT: Alzheimer's disease (AD) is a national and global epidemic with complex patho-etiology including compromised brain metabolic activity and decreased regenerative capacity. Allopregnanolone (Allo) is an investigational neuroregenerative therapeutic, currently in Phase 1b clinical trial for AD (NCT02221622,https://clinicaltrials.gov/ct2/show/NCT02221622?term=NCT02221622&rank=1). In rodent preclinical models, Allo promotes neural stem cell (NSC) proliferation and neural differentiation and improves mitochondrial function. To develop biomarkers to predict regenerative response to Allo, we have initiated proof of concept analyses to determine the impact of Allo on human induced pluripotent stem cells (iPSCs) and iPSC-derived neural cells. T-cells from a patient with familial AD due to the A431E presenilin-1 point mutation were reprogrammed via a non-integrating, non-viral method, to iPSCs. Additional iPSCs were provided by the University of California Irvine Alzheimer's Disease Research Center (UCI-ADRC) and the Institute for Memory Impairments and Neurological Disorders. Isogenic iPSCs were generated using CRISPR-Cas9. Using dual inhibition of SMAD signaling, iPSCs were differentiated to NSCs. Mitochondrial respiration and regenerative capacity were determined using metabolic analyzer and FACS. Mitochondrial respiration and proliferation analyses were conducted in AD-derived and healthy control iPSCs and NSCs. Initial data indicates that AD iPSCs have similar proliferation rates, but increased ATP production compared to healthy controls. Analyses were conducted to determine the regenerative and bioenergetic effect of Allo. In iPSC-derived NSCs, Allo increased basal mitochondrial respiration by 78% and maximal mitochondrial respiratory capacity by 35%. Initial data demonstrate that iPSCs from AD patients demonstrate a metabolic phenotype distinct from healthy controls and that Allo improves mitochondrial function of iPSC-derived NSCs. Going forward, this approach will be used to evaluate the effect of Allo on the regenerative capacity and metabolic phenotype of clinical trial participant iPSC-derived NSCs. These data will form the foundation for developing the first regenerative biomarker to determine and monitor response to neuro-regenerative therapeutics.