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Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

New Insights Into How Alzheimer's and Related Diseases Spread in the Brain

Research focuses on crucial role of tau protein in loss of brain cells

WASHINGTON, DC — Studies released today reveal important new evidence about the central role that a protein called tau plays in the progression of Alzheimer's disease, traumatic brain injury (TBI), and other disorders characterized by a steady loss of brain cells. The findings were released at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Most previous research into Alzheimer's and related diseases has focused on a protein called beta amyloid, which forms sticky plaques that are believed to strangle healthy neurons. Recently, scientists have also turned their attention to a second protein: tau. When tau is working properly in the brain, it helps with the building and functioning of neurons. When tau malfunctions, however, it creates abnormal clumps of protein fibers, known as neurofibrillary tangles, which may not only trigger cell death, but also spread rapidly throughout the brain.

Worldwide, nearly 36 million people are living with Alzheimer's or other types of dementia, according to Alzheimer's Disease International. The World Health Organization estimates that more than 10 million people sustain a TBI each year. Understanding tau's connection to these brain disorders could have implications for possible future treatments.

Today's new findings show that:

- The symptoms of both Alzheimer's disease and TBI are associated in mice with the overproduction of the same toxic form of the tau protein (Julia Gerson, abstract 482.06, see attached summary).
- Immune cells called microglia may help trigger the spread of Alzheimer's-associated toxic protein in rodents (Tsuneya Ikezu, MD, PhD, abstract 578.08, see summary attached).
- New mouse models containing both tau tangles and amyloid plaques may offer scientists a more accurate research tool for studying Alzheimer's disease (Tong Li, PhD, abstract 578.04, see summary attached).

Other recent findings discussed show that:

- Injecting tau fibrils into the brain in mice models triggers the formation and spread of tau-containing structures that lead to cell death (Diederik Moechars, PhD, presentation 482.04, see attached speaker summary).
- A drug that boosts the function of a specific type of chemical receptor in the brain is able to reverse dementia-like behavior in mice with a tau mutation associated with frontotemporal dementia (Erik Roberson, MD, PhD, presentation 578.03, see attached speaker summary).

"As this research illustrates, the tau protein plays an incredibly complex role in the development of Alzheimer's and other neurodegenerative diseases," said Sangram Sisodia, PhD, director of the Center for Molecular Neurobiology at the University of Chicago and an expert on Alzheimer's disease. "We are in the early stages of understanding the role of the tau protein, which will be crucial for developing effective preventions or treatments."

This research was supported by national funding agencies such as the National Institutes of Health as well as other private and philanthropic organizations. Find out more about the tau protein and its role in Alzheimer's and other brain diseases at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Nanosymposium: Neurogenesis and Neurotransmission in Neurodegenerative Diseases
Saturday, Nov. 15, 1–2:45 p.m., 152A, WCC

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Abstract 482.06 Summary

Lead Author: Julia Gerson (409) 772-1826
University of Texas jegerson@utmb.edu
Galveston, Texas

Alzheimer's and Traumatic Brain Injury Linked to Same Toxic Brain Protein

Findings suggest a shared cause of cognitive deficits

The symptoms of both Alzheimer's disease and traumatic brain injury (TBI) are associated with the formation and spreading of tau oligomers, a highly toxic and altered form of the brain protein tau, according to new animal research presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. In the study, mice that received tau protein extracts from people with Alzheimer's disease or mice modeling TBI showed cognitive deficits consistent with neurodegeneration.

"Our findings add to the growing evidence that tau oligomers — not tau protein in general — are responsible for the development of neurodegenerative diseases such as Alzheimer's and for damage associated with traumatic brain injury," said lead author Julia Gerson of the University of Texas Medical Branch in Galveston. "These tau anomalies may be a viable target for drug development in TBI and in prevention of neurodegenerative disease."

In the healthy brain, tau protein plays an important role in growing new brain cells and in helping those cells communicate with one another. Scientists have identified dysfunctional tau as a factor in the memory loss and other symptoms associated with both Alzheimer's disease and TBI, but they have been unsure about which specific form of tau is involved in each of the disorders. Clumps of dysfunctional tau, called tangles, appear in the brains of those with Alzheimer's disease. However, the current study implicates a different form of tau — tau oligomers, which are very small groupings of tau molecules — in Alzheimer's disease and TBI.

For their new study, Gerson and her colleagues injected tau oligomers, collected from humans with Alzheimer's disease and from rodents with TBI, into the brains of healthy mice. Later testing revealed that the mice injected with the tau oligomers from both types of brain disorders had developed memory loss and that the molecules had spread throughout the animals' brains. These findings suggest that tau oligomers have devastating consequences in both disorders.

Research was supported with funds from the Mitchell Center for Neurodegenerative Diseases, The Cullen Trust, and The Alzheimer's Drug Discovery Foundation.

Scientific Presentation**:** Tuesday, Nov. 18, 8–11:15 a.m., Room 152A

482.06, Tau oligomers from Alzheimer's disease and traumatic brain injury induce toxicity in Htau mice
J. GERSON,[1] D. CASTILLO-CARRANZA,[1] U. SENGUPTA,[1] C. LASAGNA-REEVES,[2] R. KAYED[1]; [1]University of Texas Medical Branch, Galveston, Texas; [2]Baylor College of Medicine, Houston, Texas

TECHNICAL ABSTRACT: Tau aggregation is a pathological feature of numerous neurodegenerative disorders, including Alzheimer's disease (AD), as well as traumatic brain injury (TBI). There is no effective treatment for AD, and disease burden continues to increase. TBI not only induces cognitive changes affecting millions of people, but also leads to an increased incidence of neurodegeneration later in life. Growing evidence from our lab and others suggests that tau neurofibrillary tangles are not responsible for toxicity, but rather that the oligomeric forms of tau initiate the onset and spread of disease. We have shown increased levels of tau oligomers in both AD brains and TBI rodent model brains. Using immunoprecipitation, we isolated tau oligomers from AD, fluid-percussion-injured rat and blast-injured mouse brains. Oligomers were characterized biochemically and morphologically by atomic fluorescence microscopy and were injected bilaterally in the hippocampi of mice overexpressing human tau (Htau mice). Mice were cognitively evaluated using novel object recognition and Y-maze tasks, and brains were collected following testing for analysis. We found that tau oligomers, similar to those found in Alzheimer's disease, form as a result of brain injury in two different rodent models of TBI, and brain-derived tau oligomers injected in Htau mice accelerated the onset of cognitive deficits. Biochemical and immunohistochemical analysis of mice injected with oligomers is ongoing. Tau oligomers are likely the most toxic species of tau in neurodegenerative disease, and these results suggest that they play an important role in the toxicity underlying TBI as well. Together, these findings suggest that tau oligomers may be a viable therapeutic target in TBI and in preventing the increased acquisition of neurodegenerative disease.

Abstract 578.08 Summary

Lead Author: Tsuneya Ikezu, MD, PhD (617) 414-2658
Boston University tikezu@bu.edu
Boston

Immune Cells May Help Trigger the Spread of Alzheimer's-Associated Toxic Protein

Reducing the amount of these cells halts the process in mice

New animal research released today suggests that certain immune cells in the brain play a key part in the progression of Alzheimer's disease and that halting the actions of those cells may stop that progression. The research was presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Using a special microscope technology that can locate protein structures within cells, the researchers found tau in tiny cellular vesicles, called exosomes, in Alzheimer's model mice. They also found that immune cells called microglia helped spread the tau-containing exosomes to other nerve cells. Further research revealed that the process can be stopped by either depleting the amount of microglia in the brain or by inhibiting the creation of the exosomes, findings that suggest potential approaches for treating Alzheimer's.

"We have identified important factors that help explain how neurofibrillary tangles, which are globs of the protein tau and a hallmark of Alzheimer's disease, are formed and spread throughout the brain," said Tsuneya Ikezu, MD, PhD, of Boston University. "The mechanism by which they spread is one of the hottest topics in Alzheimer's research, and halting it before the onset of memory loss and other symptoms is a promising treatment for the disease."

Research was supported with funds from Alzheimer's Art Quilt Institute, BrightFocus Foundation, and Coins for Alzheimer's Research Trust.

Scientific Presentation: Tuesday, Nov. 18, 1–3 p.m., Room 152A

578.08, Microglia and exosome-mediated spread of pathogenic tau in Alzheimer's disease
T. IKEZU,[1] H. ASAI,[2] S. IKEZU,[2] T. HAYDAR,[3] B. WOLOZIN,[1] S. KÜGLER[4]; [1]Pharmacology and Neurology, [2]Pharmacology and Experimental Therapeutics, [3]Anatomy and Neurobiology, Boston University School of Medicine, Boston, Mass.; [4]Center for Nanoscale Microscopy and Physiology of the Brain, University Medical Center Göttingen, Göttingen, Germany

TECHNICAL ABSTRACT: The neurofibrillary tangle is a pathological hallmark of Alzheimer's disease (AD) and primarily consists of hyper-phosphorylated tau protein (pTau). pTau first appears in the entorhinal cortex in the presymptomatic stage, then gradually disseminates to the hippocampal region around the onset of clinical symptoms of AD. Halting this tau spread in the asympomatic stage is a promising therapeutic approach for AD. The exosome is a small vesicle of 50-100 nm in diameter, enriched in ceramide, and is suggested to contain neuropathogenic proteins, such as prion, α-synuclein, and, recently, tau proteins. A growing body of evidence suggests that microglia contribute to tauopathy-related pathogenesis in both human and animal models. We hypothesize that microglia transduce tau aggregates into nearby neuronal cells via exosomal secretion and that inhibition of the exosome synthesis or secretory pathway reduces tau dissemination. We found that microglia efficiently phagocytose and secrete human tau aggregates in exosomes, which efficiently transduce tau aggregates in primary cultured mouse cortical neurons and induce accumulation of pTau. Moreover, we have created a novel mouse model exhibiting acute tau-spread by stereotaxic injection of adeno-associated virus expressing neuron-specific human mutant tau into the medial entorhinal cortex of mouse brain, which shows spread of human tau to the granular cell layer of dentate gyrus at 28 days post injection. This tau spread was significantly suppressed by depletion of microglia or inhibition of neutral sphingomyelinase-2, which synthesizes ceramide and regulates exosome synthesis. These results demonstrate that microglia and exosomes play significant roles in spreading pathogenic tau in mouse brain. Our findings could lead to an entirely novel paradigm for delaying the progression of disease not only in AD, but also in other tauopathies, such as frontotemporal dementia (FTD) and chronic traumatic encephalopathy.

Abstract 578.04 Summary

Lead Author: Tong Li, PhD (410) 502-5174
Johns Hopkins University tli1@jhmi.edu
Baltimore

New Mouse Model Provides More Comprehensive Model for Studying Alzheimer's

Animals have both hallmarks of the disease: tangles and plaques

Using genetic engineering techniques, researchers have created a new line of mice that mimic human Alzheimer's disease more closely than previous rodent models, potentially allowing scientists to better study the disease and search for treatments. This development was announced today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"The new mouse model will help researchers clarify the mechanisms causing the loss of nerve cells in Alzheimer's disease," said lead author Tong Li, PhD, of Johns Hopkins University in Baltimore. "It will also help researchers more effectively screen new drugs for treating Alzheimer's before testing those drugs in clinical trials."

The memory problems associated with Alzheimer's disease involve two types of abnormal groupings of proteins: tau "tangles," which form inside neurons, and amyloid plaques, which form outside neurons. In the past, research efforts have focused on finding drugs that could treat either the amyloid or the tau problem. More recently, however, it has become clear that figuring out how these clumped proteins work together to cause nerve cells to die may be the key to finding more effective treatments to slow Alzheimer's disease.

According to Li and his colleagues, the new mouse model is already revealing answers to how tau tangles and amyloid plaques interact. With the model, the researchers found that the presence of the plaques speeds up the formation and spread of the tau tangles, which then leads to cell loss, a process that may be important in the progressive death of neurons in Alzheimer's disease patients.

Research was supported with funds from the Ellison Medical Foundation, the Brain Science Institute at Johns Hopkins, and the Johns Hopkins University Neuropathology Pelda Fund.

Scientific Presentation: Tuesday, Nov. 18, 1–3 p.m., Room 152A

578.04, Progressive tauopathy-dependent neurodegeneration in mice expressing an inducible tau transgene: towards a new model of Alzheimer's disease
T. LI, J. ZHANG, A. LAU; Johns Hopkins University, Baltimore, Md.

TECHNICAL ABSTRACT: Effective therapy for Alzheimer's disease (AD), the most common form of dementia and a devastating illness for the elderly, remains a great, unmet need. For translational research and preclinical drug development, animal models that mimic the cardinal pathological features of AD will be critical. A major limitation of current mouse models is the lack of progressive AD-like neuropathology, especially the robust age-dependent neuronal loss in their brains. Here, we generated and characterized new mouse models that conditionally express the four repeat domain of human tau with the ΔK280 mutation (Tau4R-ΔK280 mice). The Tau4R-ΔK280 mice not only develop AD-like tau pathologies, but also recapitulate the age-dependent neuronal loss seen in AD. Tau4R-ΔK280 mice exhibit age- and dosage- dependent hyperphosphorylated tau aggregation with ensuing deposition of tau tangles, neuronal loss and forebrain atrophy. Importantly, deficits in working memory in these mouse models occur during the early stages of development of tauopathy. As observed in cases of AD, reactive astrogliosis is associated with severe neuronal loss in Tau4R-ΔK280 mice. Thus, we have established a mouse model of tauopathy that mimic some salient features of AD. We anticipate that our Tau4R-ΔK280 mice when crossbred to APP mice will create a mouse model of AD not only useful for studying disease mechanisms, but also amenable for pre-clinical drug screening and validation of novel therapies for AD.

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Speaker Summary (482.04)

Speaker: Diederik Moechars, PhD
Janssen Research & Development
Beerse, Belgium

+ 32 32 321-460
dmoechar@its.jnj.com

Developing a More Authentic Model of Tau Pathology

Nanosymposium: Aggregation of Amyloid, Tau, and Other Proteins
Tuesday, Nov. 18, 8–11:15 a.m., Room 152A

Brain diseases associated with the misformed protein tau, including Alzheimer's disease and frontotemporal lobar degeneration with tau pathologies, are characterized by neurofibrillary tangles (NFTs), pathological clumps comprised of tau filaments. Tau tangles are also found in progressive supranuclear palsy, cortical basal degeneration, and other related tauopathies, including chronic traumatic encephalopathy due to repetitive traumatic brain injuries sustained in sports or on the battlefield.

By using synthetic fibrils made from pure recombinant protein tau, we provide direct and compelling evidence that tau fibrils alone are entirely sufficient to recruit and convert soluble tau within cells into pathological clumps in neurons (referred to as seeding), followed by transmission of tau pathology to other interconnected brain regions (referred to as spreading) from a single injection site in an animal model of tau brain disease. Dependent on the site of injection, the pathologic clumps that develop trigger neuronal cell loss.

Young mice overexpressing mutant human tau were injected with synthetic preformed tau fibrils. These fibrils were assembled from recombinant full-length tau or truncated tau containing four microtubule-binding repeats. The synthetic tau fibrils caused rapid induction of NFT-like inclusions in the brains of the mice. These inclusions then propagated from injected sites to connected brain regions in a dose- and time-dependent manner.

Interestingly, injection of the synthetic tau fibrils into either the hippocampus or cortex led to distinctly different patterns of spreading, which is reflective of their functional connectivities. The simplest explanation for this phenomenon is that the injected pathological tau is taken up by the processes of normal neurons, where it then corrupts the tau in these nerve cells. The corrupted tau is then transported along the processes and then released and taken up by other neurons. The cycle repeats itself over and over again, thereby driving disease progression.

Where this study clearly adds further value to currently published studies is that injection of the synthetic tau fibrils into the hippocampus caused rapid induction of NFT-like inclusions that triggered strong local neuroinflammation and eventually neuronal cell loss.

We are currently exploring the mechanisms of tau aggregation, tau spreading, and the aggregated tau-induced neuronal cell loss in this newly developed model. We believe that this transmission model may more faithfully recapitulate human Alzheimer's pathogenesis than the conventional transgenic mouse models of overexpressing mutant genes that develop aggregates. Therefore, this newly developed transmission model with associated neuronal cell loss will aid in the search for disease modifying treatments for Alzheimer's and related tauopathies.

Research was supported with funds from Janssen Research & Development.

Speaker Summary (578.03)

Speaker: Erik Roberson, MD, PhD (205) 996-9486
University of Alabama at Birmingham eroberson@uab.edu
Birmingham, Ala.

Study Suggests Therapeutic Target for Second Most Common Form of Dementia

Nanosymposium: Tauopathy: Molecular Pathogenesis and Experimental Therapy
Tuesday, Nov. 18, 1–3 p.m., Room 152A

Drugs that boost the function of a specific type of neurotransmitter receptor may provide benefit to patients with the second most common type of dementia, according to research by scientists at the University of Alabama at Birmingham (UAB).

Frontotemporal dementia, known as FTD, is a devastating disease in which patients have rapid and dramatic changes in behavior, personality, and social skills. The age of onset for FTD is relatively young, usually striking patients in their mid- to late 50s. The prognosis is grim; patients quickly deteriorate and usually die about three years after diagnosis. Currently, there is no effective treatment for FTD.

The UAB research team's effort focused on mutations in certain genes, primarily in the microtubule-associated protein tau (MAPT) gene. An accumulation of tau protein is associated with Alzheimer's disease, the most common form of dementia, but little is known how tau mutations affect specific brain regions.

The UAB researchers used a new mouse model expressing human tau with an FTD-associated mutation. These mice demonstrate physical behaviors similar to those seen in humans with FTD — compulsive, excessively repetitive actions such as grooming, for example. The mice also have impaired synaptic and network function in certain brain network regions.

"We found that mutant tau impairs synapses — the connections between neurons — by reducing the size of the anchoring sites of an essential glutamate receptor, called NMDA receptors," said Erik Roberson, MD, PhD, co-director of the Center for Neurodegeneration and Experimental Therapeutics at UAB and the lead investigator for the study. "Reduction of the anchoring sites left fewer NMDA receptors available at the synapse to receive excitatory signals, thus limiting synaptic firing and network activity."

The team then employed cycloserine, a drug that is known to assist NMDA receptor function and is already approved for use by the U.S. Food and Drug Administration for tuberculosis. The drug increases opening of NMDA receptors, boosting the function of the remaining receptors at the synapse. This boost of NMDA receptor function was able to restore synaptic firing and thereby restore network activity in the animal model. The restoration of normal network activity reversed the behavioral abnormalities seen in the mice.

"This study provides mechanistic insight into how a tau mutation affects specific brain regions to impair a network," Roberson said. "It also provides a potential therapeutic target, the NMDA receptor, which appears to correct the network and behavioral abnormalities."

Roberson's team hypothesizes that increasing NMDA receptor function may benefit human FTD patients. With further preclinical validation, this hypothesis could be tested in clinical trials using the already available drug cycloserine.

Research was supported with funds from the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, the Consortium for Frontotemporal Dementia Research, and the Stephen Bechtel Fund.