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NEW TOOLS FOR ALZHEIMER'S MAY AID EARLY DIAGNOSIS AND TREATMENT

Nanotechnology, brain imaging, and new mouse strains aiding quest for detection and therapy

NEW ORLEANS — Curtailing the imminent rise in Alzheimer's disease (AD) will require early, accurate diagnostic tests and treatments, and researchers are closer to achieving these two goals. New findings in medical imaging, molecular analysis of neurological diseases, and development of treatments using mouse models were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

AD is the most common cause of dementia and currently affects 5 million people in the United States. By 2015, this number could increase to 13 million people.

Today's new findings show that:

- Changes in brain function occur many years before symptoms in people with AD; these changes could be detected by PET scans and might one day be used to identify people at risk for developing the disease (Lori Beason-Held, PhD, abstract 545.22, see attached summary).
- A new drug that targets biochemical changes in proteins improved symptoms and increased survival in a mouse model of AD, but just how it works is a mystery (Fred Van Leuven, PhD, abstract 416.08, see attached summary).
- An antibody-based probe that uses nanotechnology and magnetic resonance imaging can distinguish between diseased and non-diseased brain tissue and could lead to a test for early detection of AD (William Klein, PhD, abstract 753.21, see attached summary).
- AD, Parkinson's disease, and Dementia with Lewy Bodies have specific molecular signatures caused by epigenetics — mechanisms that determine how and when DNA is expressed — that could assist in accurate diagnosis and earlier treatment (Paula Desplats, PhD, abstract 50.17, see attached summary).
- A new mouse model for AD gives researchers more control over an Alzheimer's-related protein in mice, and could lead to better research on effective treatments (Alena Savonenko, MD, PhD, abstract 416.04, see attached summary).

"Being able to detect AD early — perhaps even before symptoms begin — is an essential pre-condition if we are to develop effective treatments that slow or stop the changes that occur in the brain during Alzheimer's. Our studies in mice already tell us this," said press conference moderator Sam Gandy, PhD, MD, of the Mount Sinai School of Medicine in New York City, an expert on AD and dementia. "Being able to distinguish AD from other neurodegenerative diseases will help us give the right treatments to the right patients."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations.

Related Presentation:

Special Lecture: **Alzheimer Mechanisms and Therapeutic Strategies**
Tuesday, Oct.16, 10–11:10 a.m., Hall D

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Abstract 545.22 Summary

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Brain Activity Appears to Change Years before the First Symptoms of Dementia

Noninvasive imaging method shows potential for early detection of Alzheimer's disease

Changes in brain function can be detected many years before people develop symptoms of age-related cognitive impairment, according to a new study. These findings could be used to predict who is at risk for developing Alzheimer's dementia years later — people who might benefit from early treatment. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The study, by lead author Lori Beason-Held, PhD, of the National Institute on Aging and colleagues examined changes in brain activity in participants from the Baltimore Longitudinal Study of Aging. Researchers used positron emission tomography (PET) to image brain function when the brain was in a resting state. Of the 121 participants, 22 developed cognitive impairment an average of 11 years after scanning began. The researchers compared brain scans of participants who eventually developed impairment with those who retained normal cognition. They found that changes in brain function can be detected many years before the onset of symptoms.

"Because treatment of Alzheimer's disease (AD) may work best before insurmountable brain changes take hold, it is important to determine early markers predictive of the disease," Beason-Held said. "Our research shows that changes in brain function, detectable with noninvasive PET scans, may be one of the early markers we need."

People who eventually developed cognitive impairment showed early differences in their brain function in frontal and parietal areas of the brain that develop the amyloid plaques and tau tangles — two anatomic hallmarks of AD. These abnormal deposits of proteins can silently develop in AD more than 10 years before cognitive symptoms emerge. Based on the study, it now appears that functional changes also occur well before symptoms are detected and in many of the same brain regions.

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

Scientific Presentation: Tuesday, Oct. 16, 9–10 a.m., Hall F-J

545.22, Changes in brain function occur many years prior to cognitive impairment
*__L. L. BEASON-HELD__, J. O. GOH, M. A. KRAUT, R. J. O'BRIEN, S. M. RESNICK; NIA/NIH, BALTIMORE, MD; Johns Hopkins Univ., Baltimore, MD

TECHNICAL ABSTRACT: It is estimated that 16 million individuals in the U.S. alone will be diagnosed with dementia by the year 2050. To develop targeted intervention strategies, there is an increasing need to identify early markers of brain change that occur prior to the onset of cognitive impairment. Here, we examine changes in resting-state brain function in participants from the Baltimore Longitudinal Study of Aging (BLSA). Using annual 15O-water positron emission tomography (PET) scans with baseline collection beginning an average of 11 years prior to impairment (mean interval from baseline to onset of impairment=10.9 ± 3.4 years; range 4-15 years), longitudinal changes in regional cerebral blood flow (rCBF) over a 7 year period were compared between participants who eventually developed cognitive impairment (n=22) and those who remained cognitively normal (n=99). Using a mixed model analysis, significant differences in rCBF change were seen prior to the onset of symptoms in those who subsequently developed impairment. These changes included greater longitudinal rCBF increases in orbitofrontal, medial frontal and anterior cingulate regions, and greater longitudinal decreases in parietal, occipital and thalamic regions. Whereas some studies have shown that increased activity occurs in posterior brain regions in the early stages of impairment, we show that anterior regions increase activity prior to the onset of symptoms. Our results suggest that functional changes can be detected many years prior to development of cognitive impairment, and that these changes occur in regions that develop early pathologic changes in Alzheimer's disease.

Abstract 416.08 Summary

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Compound Improves Alzheimer's Disease Symptoms in Mice

But why it works remains a mystery

Mice used to study Alzheimer's disease (AD) show improvements after treatment with a compound that targets biochemical changes in certain proteins. The findings point to new directions in research for prevention and treatment of AD, adn were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The study, presented by lead author Fred Van Leuven, PhD, with the Experimental Genetics Group at KULeuven Belgium, worked with two strains of mice bred to produce a defective human version of Tau, a protein that normally lends structural stability to nerve cells, but is defective in AD and a host of other brain diseases. Both strains of mice have shortened life spans and exhibit symptoms related to AD.

Tau protein is thought to be modified by the addition of a sugar-based molecule, through a reversible process called O-GlcNAc-ylation ("oh-glue-nak-ilation"). But O-GlcNAc-ylation levels are lowered in the brains of people with AD, so Van Leuven and colleagues treated the mice with a compound to ramp it up.

The treatment eased motor problems and extended life. In one mouse strain, three times more treated mice survived at age 9.5 months than untreated mice. Surprisingly, however, the expected biochemical changes in the Tau protein did not occur, raising questions about how the treatment worked.

"The clinical benefits were impressive, but those benefits occurred without the expected change in the Tau protein," Van Leuven said. "This is intriguing and opens potential new avenues for understanding, and eventually treating, the neurodegenerative defects associated with Tau."

Research was supported with funds from Fonds Wetenschappelijk Onderzoek (Fund Scientific Research), Innovatie Wetenschap & Techniek, European Union, and Leuven University.

Scientific Presentation: Monday, Oct. 15, 1–3:30 p.m., Room 262

416.08, Increasing O-GlcNAc-ylation of brain proteins counteracts negative effects of amyloid and Tau.
*__F. VAN LEUVEN__, P. BORGHGRAEF, H. DEVIJVER, B. LECHAT, H. GIJSEN, C. MENUET, G. HILAIRE, D. MOECHARS; Human Genet., Exptl. Genet. Group - LEGTEGG, Leuven, Belgium; Janssen-R&D, Beerse, Belgium; MP3-Respiration, Marseille, France

TECHNICAL ABSTRACT: *Background.* Conjugation of β-N-acetylglucosamine to S/T residues is a reversible post-translational modification controlled by two unique enzymes: O-GlcNAc transferase (OGT) and β-N-acetyl-glucosaminidase (OGA). Hundreds of proteins are O-GlcNAc-ylated but details of target specificity, biochemical characteristics and physiological and pathological significance remain largely unknown in vivo, particularly in CNS. Tau is important for microtubule stability and transport, causing synaptic defects and neurodegeneration by unknown molecular mechanisms. In Alzheimer's disease, accumulating amyloid peptides aggravate phosphorylation of Tau by activation of both GSK3 isozymes, modeled in our bigenic mice biAT and biGT mice (Terwel et al, 2008). Tau.P301L mice suffer cognitive deficits (4-6 mo), motor dysfunction (6-8 mo), loss of bodyweight, ending with precocious death (8-12 mo, mean 9.5 mo). Aggregates of Tau in brainstem correlate with upper-airway dysfunction and death (Dutschmann et al., 2010; Menuet et al, 2011a,b). Increasing O-GlcNAc-ylation by OGA inhibition was explored here in vivo in old Tau.P301L and young biAT mice.
Results. Chronic treatment of ageing Tau.P301L mice mitigated loss in body-weight and motor deficits. Moreover, 3-fold more treated Tau.P301L mice survived at the pre-fixed endpoint at age 9.5 months. In addition, O-GlcNAc-ase inhibition significantly improved breathing parameters of Tau.P301L mice, pharmacologically underpinning correlation of mortality to upper-airway defects. Biochemically, O-GlcNAc-ylation of brain proteins increased rapidly and stably by systemic inhibition of OGA. Conversely, no biochemical evidence was obtained that protein Tau.P301L was O-GlcNAc-ylated, nor was its phosphorylation markedly affected. Similarly, chronic OGA-inhibition of young biAT mice (3 mo) for 125 days prevented early mortality, improved general condition and decreased anxiety. Also in this model, the phosphorylation of protein tau was not markedly affected.
Conclusion. Pharmacologically increasing protein O-GlcNAc-ylation markedly improved clinical condition, and prolonged survival of ageing Tau.P301L mice and young biAT mice with combined amyloid and Tau expression. Surprisingly, in both models clinical benefits were not reflected by biochemical parameters of protein Tau. The pharmacological target of the OGA inhibitor must be located downstream in the pathological cascade initiated by protein Tau.P301L, opening a novel venue for understanding and eventually treat neurodegeneration mediated by protein Tau.

Abstract 753.21 Summary

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New MRI Probe Could Lead to Test for Early Detection of Alzheimer's Disease

Antibody-based probe distinguishes between Alzheimer's disease and normal brain tissue

A nanotechnology-based brain imaging probe can detect a small toxin active early in the course of Alzheimer's disease (AD). Initial success in rodent and laboratory studies could lead to a unique human diagnostic, according to findings presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

A major hurdle to development of effective AD treatments is the inability to detect the disease early. The work, reported by lead author William Klein, PhD, of Northwestern University, could finally allow for early detection of AD, and provide a new tool for evaluating experimental drugs.

"We have created a probe that targets a unique marker of Alzheimer's disease," Klein said. "This technology is a promising tool for early AD diagnosis and for evaluating the efficacy of investigational new drugs at early stages of the disease."

The new probe targets toxins called amyloid beta oligomers, which appear early in the disease and may be responsible for initiating memory loss in AD. The probe uses antibodies that bind strongly and specifically to the toxic oligomers in the brain. The antibodies are fused with magnetic nanoparticles so that they show up in magnetic resonance imaging (MRI) scans. The promising research is early in development, but it has been found to distinguish Alzheimer's from non-Alzheimer's brain tissue in laboratory experiments. The researchers are designing a way to deliver the antibody probe to people via a nasal spray.

Research was supported with funds from National Institutes of Health, National Science Foundation, the Veterans Administration, and the Alzheimer's Association.

Scientific Presentation: Wednesday, Oct.17, 8–9 a.m., Hall F-J

753.21, Development of a molecular MRI probe for early diagnosis of Alzheimer's disease and evaluation of investigational new drugs
*K. L. VIOLA, J. SBARBARO, R. SUREKA, M. DE, H. JOSHI, N. B. CHAUHAN, C. LU, J. PHAN, P. T. VELASCO, P. N. LACOR, V. P. DRAVID, **W. L. KLEIN**; Neurobio., Material Sci., Northwestern Univ., Evanston, IL; Jesse Brown VA; Univ. of Illinois at Chicago, Chicago, IL

TECHNICAL ABSTRACT: This study addresses the need to develop diagnostic imaging of early-stage Alzheimer's disease (AD), when newly emerging vaccines and other treatments can be truly effective. Due to the reliance on probes that target amyloid plaques, recent advances in AD diagnostic imaging methods can only be used to confirm diagnosis and evaluate investigational new drug (IND) effects at late-stage AD. We have developed a new approach that has the potential to image synaptotoxic Aβ oligomers. Because toxic Aβ oligomers (also referred to as "ADDLs") appear early in the disease and are now widely regarded as responsible for instigating AD memory loss, they offer an excellent target for molecular diagnosis. Our approach uses a powerful nanotechnology-based brain imaging strategy. We have derivatized aqueous-stable magnetic nanostructures (MNS) with an oligomer-specific antibody (NU4). The resulting probe (NU4MNS) detects Aβ oligomers with high affinity and specificity, both in solution and bound to synapses in primary hippocampal neuronal cultures. The NU4MNS probe is equivalent to the parent monoclonal antibody in being able to discriminate AD human frontal cortex sections from aged controls by immunofluorescence microscopy. Most importantly, the NU4MNS probe provides a pronounced MRI signal that is disease-dependent, clearly distinguishing probable AD from non-demented control tissue. The data establish that human disease-dependent signal can be obtained by targeting Aβ oligomers ex vivo. To bypass the blood brain barrier for follow up studies in vivo, we have developed a novel means to deliver the probe to the brain using intranasal injection. So far, intranasal delivery of NU4 conjugated to wheat-germ agglutinin (WGA) has been found to provide an antibody dose that prevents memory failure in a transgenic mouse AD model (Chauhan et al, 2012, AAIC Vancouver). Overall, the data provide proof of concept that magnetic nanostructures derivatized with an oligomer-specific antibody yield a unique MRI probe that provides an Aβ oligomer-dependent signal in culture and human AD brain tissue. The new target, the new probe, and the new means of delivery provide an innovative solution to answer the need for diagnostic imaging of early AD. This work has the potential to provide the first imaging tool for early AD diagnosis and for use in evaluating efficacy of investigational new drugs at early-stages of the disease.

Abstract 50.17 Summary

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Gene "Signatures" Could Help Distinguish Alzheimer's Disease from Other Disorders

Differences in genes that reshape DNA and change gene expression patterns are found in brain disorders

Researchers have found abnormalities caused by "epigenetics" in three brain disorders — Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), and Parkinson's disease (PD) — which could also represent their molecular signatures. Because symptoms of these diseases are very similar, these findings could aid in accurate diagnosis to start the correct treatments earlier. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The study, led by author Paula Desplats, PhD, at the University of California, San Diego, used brain autopsy samples from people with the three different diseases, and from healthy people of similar ages. The researchers looked at changes in the activity of 84 epigenetic-related genes whose action can change the structure of the DNA — and thus the normal function of other genes. Epigenetics are mechanisms that dictate when and how the blueprint code of DNA should be executed and can change in response to a person's environment, including age and diet.

"We observed abnormal expression of genes that reshape the DNA, which means that epigenetic changes are part of the pathology of these diseases," Desplats said. "Since the patterns of the changes are unique to each disease, they could potentially aid in accurate diagnosis of neurodegenerative disorders that present similar symptoms, leading to prompt intervention and improved treatments."

AD is the most common cause of dementia. PD is the second-most common neurodegenerative disorder affecting the elderly, and is marked by loss of muscular control. DLB is the second most common cause of dementia and also produces mild Parkinson's-like symptoms.

All three diseases showed common changes in three epigenetic genes, but importantly, another group of genes was specifically altered in each of the diseases. This could be a useful "biomarker" of a neurological disorder. The researchers also found that each of the three diseases was associated with the abnormal activation of specific genes.

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

Scientific Presentation: Saturday, Oct. 13, 1–2 p.m., Hall F-J

50.17, Epigenetic signature of Alzheimer's, Parkinson's and Dementia with Lewy bodies: Common marks and specific alterations in chromatin modifiers.
*__P. A. DESPLATS__, P. PATEL, S. MICHAEL, A. ADAME, E. MASLIAH; Neurosciences, Neurosciences and Pathology, Univ. of California San Diego, La Jolla, CA

TECHNICAL ABSTRACT: Alterations in epigenetic mechanisms, including DNA methylation and histone lysine methylation, are well characterized in the disregulation of brain transcriptomes in mood and psychosis disorders like depression and schizophrenia. While we have previously reported epigenetic disregulation in Parkinson's disease, the extent of such alterations and their involvement in the pathology of the main neurodegenerative disorders remain to be fully elucidated. We investigated here the expression of 84 key genes encoding enzymes known or predicted to modify genomic DNA and histones in postmortem frontal cortex samples from patients with confirmed diagnosis of Alzheimer's disease (AD), Parkinson's disease (PD) and Dementia with Lewy bodies (DLB) in comparison to age and sex matched healthy control subjects (n=6-8/group). We observed disregulation of epigenetic factors in all the tested groups, with 13 genes being altered in AD, 17 in PD and 20 in DLB. Gene ontology analysis revealed that histone modifications were the most affected functional groups, in particular histone lysine methylation, an epigenetic modification that has pivotal roles in chromatin remodeling and gene expression regulation. We found 3 transcriptional alterations common for all the studied diseases: upregulation of KAT2A (K(lysine) acetyltransferase 2A) and downregulation of ESCO1 (N-acetyltransferase) and NCOA1 (Nuclear Receptor coactivator 1). In addition, we detected signature transcriptional alterations for each disease. AD cases presented upregulation of AURKC and downregulation of HAT1, KAT2B, MBD2, RFN20. DLB brains showed upregulation of AURKA, EHMT2, HDACs 6, 7 and 10, KDM1A and ATF2. PD cases were characterized by upregulation of CDYL, ESCO2, HDACs 5 and 11, and KDM5C and downregulation of SETD6. Importantly, similar alterations in a subset of transcripts was common for AD and DLB, that might represent a signature of dementia-associated disorders; while a different group of genes was disregulated in both, DLB and PD, which present with alpha-synuclein accumulation. The lowest similarities in transcriptional disregulation were found

between AD and PD, which pathologically are less related. In summary, we identified significant disregulation in the expression of chromatin modifiers in a range of neurodegenerative diseases that present with and without associated dementias. These results highlight the involvement of epigenetic mechanisms in the pathology of these highly prevalent disorders in the elderly and points out common and particular signatures that might aid in differential diagnosis as biomarkers or in the discovery of novel therapeutic targets.

Abstract 416.04 Summary

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New Mouse Model Could Improve Drug Development Research for Alzheimer's Disease

Researchers control timing of brain plaques development in new mouse strain

An improved mouse model of Alzheimer's disease could help researchers develop drugs that halt or reverse memory loss and other disease symptoms. This model enables scientists to control the production of the amyloid precursor protein, the protein which leads to the brain plaques of Alzheimer's disease. Based on the research, animals that begin producing the protein later in development appear to more accurately model human disease and thus aid in the development of effective treatments. This research was presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The study, presented by senior author Alena Savonenko, MD, PhD, of the Johns Hopkins University School of Medicine, used a new Alzheimer's disease mouse model designed by David Borchelt, PhD, and Joana Jankowsky, PhD. In the model, mice have a specially constructed gene for amyloid precursor protein, the protein that creates the plaque found in the brain of patients with Alzheimer's disease. An experimental drug given to the mice prevents the gene from making the amyloid precursor protein.

Savonenko and colleagues raised mice to produce the amyloid precursor protein either earlier or later in life. At the age of 13 months, all mice had brain plaques and showed memory defects in maze tests. When production of the protein was shut off — a situation that might mimic the effect of a potential Alzheimer's disease treatment — memory problems were unaffected in the mice that had been producing the protein their entire lives. However, mice that produced protein only later in life responded with improved performance on memory tests.

"Our findings suggest that current mouse models, which make high amounts of amyloid precursor protein starting early in life, could miss the effects of experimental drugs," Savonenko said. "The new mouse model could allow scientists to use mice more effectively in testing new therapies for Alzheimer's disease."

Research was supported with funds from the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging.

Scientific Presentation: Monday, October 15, 1–2 p.m., Hall F-J

416.04, Effects of acute inhibition of APP/Aβ production in adulthood are modulated by APP overexpression during development
***A. V. SAVONENKO**, T. MELNIKOVA, S. FROMHOLT, H. KIM, D. LEE, E. CHO1, D. BORCHELT;

TECHNICAL ABSTRACT: The amyloid precursor family of proteins is of considerable interest, both because of their role in Alzheimer's disease pathogenesis and their normal physiological functions. Data accumulated in Alzheimer's disease (AD) models suggest that APP/Aβ overproduction can results in a number of behavioral effects. In numerous APP transgenic models, particularly in high expressing lines, cognitive deficits coexist with hyperactivity. In what extent the cognitive deficits and hyperactivity share the same mechanisms is unclear. By using conditional TetOff-APP transgenic mice in which expression of APP can be halted by doxycycline (DOX) we tested the effects of early and late onset of APP overexpression on cognitive and exploratory behaviors in adulthood. A tTa-responsive chimeric mouse/human APP695swe/ind mice (Line 107) were created as described (Jankowsky et al., 2005) and crossed to CaMKIIα –tTa mice (Jackson). Double transgenic APP x tTa males on C57BL/6J background were then bred to FVB/NJ females (Jackson) to receive F1 progeny for behavioral testing. Half of APP x tTa Tg mice and their control littermates were kept on a DOX diet until one month of age (referred to as a Late Expression group) or on a regular diet allowing for early APP expression (an Early Expression group). The behavioral analysis of hyperactivity was comprised of a battery of tests to assess novelty-induced exploratory behavior in different environments. Testing of spatial recognition memory was conducted in a two-trial Y maze with a 25-min delay, whereas long-term spatial memory was tested in a multi-trial T water maze after a 24-hr delay. Both, Early and Late Expression groups were tested at 13.5 mo of age at which point they accumulated similar amount of Aβ plaques (tested by a Thioflavin-S staining) and similar levels of Aβ peptides (tested by ELISA). Both groups showed deficits in the spatial recognition memory whereas the long term memory was not different from age-matched controls. Acute inhibition of APP/Aβ production (7 days on DOX) ameliorated hyperactivity in both, Early and Late Expression groups. Significantly higher and generalized (over different tasks) hyperactivity in the Early Expression group, however, indicated that production of APP/Aβ during postnatal stages of development sensitizes to the effects of APP overexpression during adulthood. Importantly, acute inhibition of APP/Aβ production rescued the deficits in spatial recognition memory only in the Late Expression group. These data indicate that in contrast to a hyperactivity phenotype, the effects of acute inhibition of APP/Aβ production on cognitive deficits may be modulated by APP overexpression during development.