

Alzheimer's Disease



NEWS



RESEARCH HIGHLIGHTS



INTERVIEW



Epilepsy drug may improve cognitive function in a condition that often leads to Alzheimer's disease

A group of researchers at Johns Hopkins University (MD, USA), have found an anti-convulsant drug to improve memory and brain function in adults with the condition amnesic mild cognitive impairment (aMCI), which often leads to Alzheimer's disease (AD). These results were presented at the Alzheimer's Association International Conference (AAIC) in Paris, France.

Amnesic mild cognitive impairment is characterized by episodic memory impairment in the absence of clinical dementia. This condition often represents a transitional stage between normal aging and AD. Researchers have proposed that excess brain activity in people with aMCI may contribute to brain dysfunction that underlies memory loss. This is contrary to the previous theory that hyperactivity observed in the aMCI brain is a compensatory mechanism for impaired ability to form new memories.

The drug used in this study, levetiracetam, is an approved drug that is currently prescribed as an anticonvulsant for epileptic patients. This drug works by binding to a synaptic vesicle protein, SV2A, and impeding nerve conduction. If excess activity were to contribute to memory loss (and eventually AD) in aMCI patients, as demonstrated in this study, this could open the gates for treatment with currently available neuroinhibitory drugs, such as levetiracetam.

This study included 34 adults (some with aMCI and some without). Each participant completed a sequence of two treatment phases lasting 2 weeks each. A low dose of levetiracetam was administered during one phase and a placebo during the other. The researchers evaluated the subjects' memory and conducted functional MRI brains

scans after each treatment phase. These scans were used to map brain activity during a memory task, allowing the researchers to compare each individual's status both on and off the drug.

As expected, it was found that aMCI subjects who were given the placebo had excess activity in the hippocampus, which is the part of the brain essential for memory. Interestingly, hippocampal activity was reduced to the same level as that of the control subjects in aMCI participants who had been taking levetiracetam for 2 weeks. The drug also improved aMCI participants' performance in a memory task, to the extent that they performed to the same level as the controls.

Michela Gallagher, principal investigator of the study, explains, "Because some of the physiology that creates Alzheimer's disease in the brain is driven by greater brain activity, this excess activity might be like having your foot on the accelerator if you are on the path to Alzheimer's. So the next step in this line of research will be to test that idea to see whether reducing excess activity might actually slow progression to Alzheimer's for patients with aMCI."

This study warrants further research into the long-term benefits of levetiracetam use, and whether it has a capability to slow the progression of Alzheimer's disease.

Sources: Johns Hopkins University: Drug improves brain function in condition that leads to Alzheimer's; <http://ireleases.jhu.edu/2011/07/20/drug-improves-brain-function-in-condition-that-leads-to-alzheimers/> (Accessed 28 July 2011); Doody RS, Ferris SH, Salloway S et al. Identifying amnesic mild cognitive impairment in primary care: a feasibility study. Clin. Drug Investig. 31(7), 483-491 (2011).



New Alzheimer's drug in Phase I clinical trials may target both amyloid and tau pathology

The biopharmaceutical company Anavex Life Sciences Corp, NJ, USA, recently announced at the Alzheimer's Association International Conference (AAIC) 2011 in Paris, France that the company's lead drug candidate for Alzheimer's disease (AD), ANAVEX 2-73, could potentially target both tau and amyloid pathologies in the Alzheimer's brain. These findings were obtained from studies on nontransgenic AD mouse models.

People with AD typically bear two main hallmark features in their brains. The first is a peptide called amyloid β , which forms in plaques. This pathology has been pharmacologically targeted most often in past research. The second is hyperphosphorylated tau protein, which forms in aggregates called neurofibrillary tangles. There are currently no drugs on the market that are known to target both of these pathologies.

ANAVEX 2-73 is a mixed σ -1 agonist, muscarinic-1 agonist and a muscarinic-2

and -3 antagonist. It is the first of a new class of AD drugs being developed by Anavex Life Sciences Corp, called the aminotetrahydrofurans. ANAVEX 2-73 has already demonstrated neuroprotection in animal models. Results imply that the drug could potentially prevent memory deficits.

Novel findings announced at the AAIC involve the theory behind tau hyperphosphorylation. The formation of neurofibrillary tangles may be triggered by the actions of certain key enzymes, such as an increase in glycogen synthase kinase (GSK)-3 β . It appears that ANAVEX 2-73 increases levels of the serine/threonine protein kinase, Akt, and decreases levels of GSK-3 β , which may consequently decrease tau pathology. Tangui Maurice (University of Montpellier, France) who is a member of the Anavex Scientific Advisory Board, explains, "It may be that Akt increase and GSK-3 β decrease is a protective mechanism in AD and is restored

by mixed σ -1 and muscarinic agents such as ANAVEX 2-73."

Cameron Durrant, Executive Chairman of Anavex adds, "These groundbreaking data may suggest a unique dual mechanism for ANAVEX 2-73 that could potentially ameliorate both amyloid toxicity and tauopathy through one approach. We eagerly await results from the ANAVEX 2-73 Phase I clinical trial, which is scheduled for completion soon."

The Phase I clinical trial is being conducted in Germany in collaboration with the clinical research organization, ABXCRO, and the Technical University of Dresden. Researchers hope that this trial will determine the maximum tolerated single dose, safety and pharmacokinetics of ANAVEX 2-73.

Source: Anavex Life Sciences Corp. Anavex presents data on potential dual utility of ANAVEX 2-73 in both amyloid and tau pathology. http://anavex.com/press_release_2011_07_25.html (Accessed 28 July 2011)

New guidelines available for genetic counseling and testing for Alzheimer's disease

An updated set of practice guidelines surrounding the genetic testing for Alzheimer's disease has been published in the June issue of *Genetics in Medicine*.

Early-onset Alzheimer's disease (EOAD), the familial form of Alzheimer's disease (AD), has three known genes affect an individual's likelihood of developing AD: the *APP* gene and two presenilin genes (*PSEN-1* and *PSEN-2*). People possessing of any of these genes will tend to develop AD before the age of 60 years, and come from families where other members also have early-onset AD. On average, first-degree relatives will have a 50% risk of inheriting the disease.

Currently only one gene is known to be associated with late-onset AD: *APOE*. This comes in three forms, with the highest risk

for AD coming from the *APOE4* type. The effects of this gene are much less definitive than that of the EOAD-linked genes, and even if an individual possesses two copies of the high-risk subtype, *APOE4*, they still may not develop AD.

Owing to the complicated genetic nature of AD, clinicians are often tentative when addressing the genetic risks of their patients for developing AD. The new practice guidelines provide clinicians with a framework for assessing their patients' genetic risk for Alzheimer's disease, and hence identify which individuals may benefit from genetic

testing, Jill Goldman, Columbia University (NY, USA), who authored the guidelines, explains to *Therapy*: "The guidelines were designed for physicians and counselors who do not specialize in neurogenetics to assist them in counseling for autosomal dominant and familial AD and give a gold standard for genetic testing."

Genetic testing for AD is generally warranted for EOAD when the family history indicates that an autosomal dominant gene is present. Goldman discusses the potential usage of genetic testing for EOAD: "Presymptomatic testing is a very difficult



thing to do and most at-risk people do not choose to do it. However, for some people, presymptomatic testing will allow family planning (sometimes using preimplantation genetic diagnosis to avoid passing the gene to offspring) and life-planning ... the purpose of pretest genetic counseling is to help people make informed decisions about testing.”

When asked about testing for late-onset AD, Goldman replied, “Testing for LOAD is an entirely different story. The only gene that can be tested right now is *APOE* which is a risk factor gene, not a determinant gene ... testing *APOE* is not advocated because it will not give much new information ... until there are better biomarkers which can demonstrate early disease stages and treatments, we

feel that *APOE* testing does not provide enough information to be recommended. However, some people may still wish to be tested because they want any available information.” *APOE* testing is now available via direct-to-consumer companies; therefore, Goldman notes that the new guidelines should help physicians understand the implications and limitations of this testing if their patients come to them with results.

Sources: Alzheimer’s Society. *Genetics and dementia*: http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=168 (Accessed 29 July 2011); Goldman JS, Hahn SE, Catania JW et al. *Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors*. *Genet. Med.* 13(6), 597–605 (2011).

Brain imaging shows promise for detecting amyloid burden in Alzheimer’s disease

A recent study, published online in the *Archives of Neurology*, has further demonstrated the utility of fluorine-18-labeled radiotracers used with PET in detecting and quantifying β -amyloid in the brain, a pathological hallmark of Alzheimer’s disease.

In the former, the researchers working across multiple research imaging centers, aimed to characterize florbetapir F 18 measurements of fibrillar β -amyloid ($A\beta$) in a large clinical cohort of 68 participants with probable Alzheimer’s disease (AD), 60 patients with mild cognitive impairment (MCI) and 82 older healthy controls. Cerebral-to-whole-cerebellar florbetapir standard uptake value ratios (SUVRs) were calculated to allow comparison of mean cortical SUVRs. Pathological amyloid thresholds and SUVRs were calibrated based on separate antemortem PET and postmortem neuropathology data from 19 end-of-life patients.

All of the participant groups had significantly different mean cortical florbetapir SUVRs; the highest were in individuals with probable AD (1.39) and the lowest in

healthy controls (1.05). The same pattern was found in comparison of percentage meeting levels of amyloid associated with AD by SUVR criteria, and in percentage meeting SUVR criteria for the presence of any identifiable $A\beta$. Florbetapir uptake increased with age in healthy individuals and was higher in those who carried the *APOE-4* allele.

“...florbetapir PET can distinguish clinical stages of Alzheimer’s disease, and can identify amyloid pathology in a percentage of cognitively normal individuals over the age of 55.”

The study by Fleisher *et al.* builds from a previous study and confirms the ability of florbetapir-PET SUVRs to characterize amyloid levels in clinically probable AD, MCI, and older healthy control groups using continuous and binary measures of fibrillar $A\beta$ burden. This latest study confirms the ability of florbetapir PET “to distinguish clinical syndromes of AD, as well as identify the

degree of abnormality seen in normal aging populations – potential preclinical AD”, explains lead author Adam Fleisher, associate director of brain imaging at Banner Alzheimer’s Institute (Phoenix, AZ, USA). Moreover, the study “also introduces thresholds of florbetapir PET levels associated with having ‘any amyloid’ in the brain, or levels associated with pathologically proven dementia of the Alzheimer’s type”, he adds.

He concludes that “florbetapir PET can distinguish clinical stages of Alzheimer’s disease, and can identify amyloid pathology in a percentage of cognitively normal individuals over the age of 55”. The study “presents compiled data for several registered trials documenting its ability to distinguish between diagnostic groups, and establishes clinically relevant thresholds of PET activity.”

Source: Fleisher AS, Chen K, Liu X et al. *Using positron emission tomography and florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease*. *Arch. Neurol.* doi: 10.1001/archneurol.2011.150 (2011) (Epub ahead of print).



Combination therapy may provide cognitive benefit to Alzheimer's patients

A group of experts have agreed there is strong evidence that Alzheimer's disease (AD) patients benefit from combination therapy with memantine and cholinesterase inhibitors. This was announced in a satellite symposium held in conjunction with the Alzheimer's Association International Conference (AAIC) 2011 in Paris, France. The experts included Alireza Atri (Massachusetts General Hospital, MA, USA), Patrizia Mecocci (University of Perugia, Italy), Jörg Schulz (University Hospital Aachen, Germany) and Jean-Marc Orgogozo (University Hospital Pellegrin, France).

Memantine is a noncompetitive NMDA receptor antagonist, which acts by preventing reuptake of glutamate at synapses in the brain. This drug is frequently prescribed for mild-to-severe AD. Cholinesterase

inhibitors (ChEIs) work by blocking the breakdown of the neurotransmitter, acetylcholine, which in turn improves neural transmission in the brain. The ChEIs prescribed for AD are galantamine, rivastigmine and donepezil. Experts have proposed that theoretical considerations and pre-clinical observations suggest that memantine and ChEIs have a synergistic effect in reducing cognitive decline.

In practice, combination therapy has been found to be particularly effective in helping patients to retain their verbal and nonverbal skills, which are essential for patients to express their needs and sustain interaction. A previous clinical trial demonstrated that memantine with donepezil significantly reduced the decline in moderate-to-severe AD patients' ability to communicate, compared with donepezil use alone.

Scientists at the symposium concluded that memantine and ChEIs slow the decline in cognition associated with AD. Combination treatment with memantine and ChEIs is a therapeutic option that combats just the symptoms of AD; it has been proposed that until disease-modifying therapies are developed, this may be the most effective treatment option to optimally preserve cognition and the ability to communicate.

Source: Alzheimer's association. Alzheimer's association international conference corporate symposia – non CME. www.alz.org/aaic/non-CME.asp (Accessed 28th July 2011); Satellite symposium "Alzheimer's disease: understanding and overcoming treatment challenges" chaired by Jean-Marc Orgogozo, held in conjunction with the Alzheimer's Association International Conference 2011, 19 July 2011, Paris, France.

About the News and Views

The News and Views highlights some of the most important events and research. If you have newsworthy information, please contact: Laura McGuinness, Editor, *Therapy*

Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK; Tel.: +44 (0)20 8371 6090;

Fax: +44 (0)20 8343 2313; l.mcguinness@futuremedicine.com