Modulating Brain’s Stress Circuitry Might Prevent Alzheimer’s Disease

By Scott LaFee
November 16, 2015

In a novel animal study design that mimicked human clinical trials, researchers at University of California, San Diego School of Medicine report that long-term treatment using a small molecule drug that reduces activity of the brain’s stress circuitry significantly reduces Alzheimer’s disease (AD) neuropathology and prevents onset of cognitive impairment in a mouse model of the neurodegenerative condition.

The findings are described in the current online issue of the journal Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association.

The results underscore the complexity and diversity of AD, whose causes appear to be a mix of genetic, lifestyle and environmental factors. Previous research has shown a link between the brain’s stress signaling pathways and AD. Specifically, the release of a stress-coping hormone called corticotropin-releasing factor (CRF), which is widely found in the brain and acts as a neurotransmitter/neuromodulator, is dysregulated in AD and is associated with impaired cognition and with detrimental changes in tau protein and increased production of amyloid-beta – protein fragments that clump together and trigger the neurodegeneration characteristic of AD.

“Our work and that of our colleagues on stress and CRF have been mechanistically implicated in Alzheimer’s disease, but agents that impact CRF signaling have not been carefully tested for therapeutic efficacy or long-term safety in animal models,” said the study’s principal investigator and corresponding author Robert Rissman, PhD, assistant professor in the Department of Neurosciences and Biomarker Core Director for the Alzheimer’s Disease Cooperative Study (ADCS).

Continued on next page...
Mouse study cont’d.....

“The novelty of this study is two-fold: We used a preclinical prevention paradigm of a CRF-antagonist (a drug that blocks the CRF receptor in brain cells) called R121919 in a well-established AD model – and we did so in a way that draws upon our experience in human trials. We found that R121919 antagonism of CRF-receptor-1 prevented onset of cognitive impairment and synaptic/dendritic loss in AD mice.”

In other words, the researchers determined that modulating the mouse brain’s stress circuitry (without actually changing the normal response) mitigated generation and accumulation of amyloid plaques widely attributed with causing neuronal damage and death. As a consequence, behavioral indicators of AD were prevented and cellular damage was reduced. The mice began treatment at 30-days-old – before any pathological or cognitive signs of AD were present – and continued until six months of age.

One particular challenge, Rissman noted, is limiting exposure of the drug to the brain so that it does not impact the body’s ability to response to stress. “This can be accomplished because one advantage of these types of small molecule drugs is that they readily cross the blood-brain barrier and actually prefer to act in the brain,” Rissman said. Drugs like R121919 were originally designed to treat generalized anxiety disorder, irritable bowel syndrome and other diseases, but failed to be effective in treating those disorders, they wrote.

“Rissman’s prior work demonstrated that CRF and its receptors are integrally involved in changes in another AD hallmark, tau phosphorylation,” said William Mobley, MD, PhD, chair of the Department of Neurosciences and interim co-director of the Alzheimer’s Disease Cooperative Study at UC San Diego. “This new study extends those original mechanistic findings to the amyloid pathway and preservation of cellular and synaptic connections. Work like this is an excellent example of UC San Diego’s bench-to-bedside legacy, whereby we can quickly move our basic science findings into the clinic for testing,” said Mobley.

Rissman said R121919 was well-tolerated by AD mice (no significant adverse effects) and deemed safe, suggesting CRF-antagonism is a viable, disease-modifying therapy for AD. Rissman noted that repurposing R121919 for human use was likely not possible at this point. He and colleagues are collaborating with the Sanford Burnham Prebys Medical Discovery Institute to design new assays to discover the next generation of CRF receptor-1 antagonists for testing in early phase human safety trials.

“More work remains to be done, but this is the kind of basic research that is fundamental to ultimately finding a way to cure – or even prevent – Alzheimer’s disease,” said David Brenner, MD, vice chancellor, UC San Diego Health Sciences and dean of UC San Diego School of Medicine. “These findings by Dr. Rissman and his colleagues at UC San Diego and at collaborating institutions on the Mesa suggest we are on the cusp of creating truly effective therapies.”

Co-authors include Cheng Zhang, Setareh H. Moghadam, Louise Monte, Shannon N. Campbell and Eliezer Masliah, UC San Diego; Ching-Chang Kuo, University of Oregon; Kenner C. Rice, National Institutes on Drug Abuse and Alcohol Abuse and Alcoholism; and Paul E. Sawchenko, Salk Institute for Biological Studies.

Funding for this research came, in part, from the National Institutes of Health (grants AG032755, AG047484, DK026741, and AG010483), the Alzheimer’s Art Quilt Initiative; the Alzheimer’s Association, The Leona M. and Harry B. Helmsley Charitable Trust and the Clayton Medical Research Foundation.
It is now widely recognized that Alzheimer’s disease (AD) is associated with insulin resistance and impaired ability to metabolize glucose. However, ketone bodies, the products of fat metabolism, can serve as a “backup” fuel for neurons when glucose is unavailable. Thus, a diet high in fat and low in carbohydrates may provide improved nourishment for the brain in early AD, and may slow or even reverse cognitive decline. Aim 1 of this study is to establish the feasibility of implementing a ketogenic, modified Atkins diet (MAD) in older adults with mild cognitive impairment (MCI) or early AD. Aim 2 is to determine whether adherence to the MAD results in better cognitive test scores than adherence to a non-ketogenic control diet. Aim 3 is to assess the role of apolipoprotein E (ApoE) genotype in participants’ response to the MAD.

Participants will be 50 people, age 60 or older, with MCI or mild probable AD. Each will have a study partner who is cognitively healthy, lives with the participant, and can help him/her adhere to the diet. Participants will be randomly assigned to a 12-week trial of either the MAD or a control diet based on the National Institute on Aging’s recommendations for senior nutrition. A research dietitian will teach participants and partners their new diets and monitor participants’ adherence with food logs and urine ketone testing. After an initial baseline visit, participants will complete four in-person assessments. We hypothesize that the MAD will be feasible and well tolerated by seniors with MCI and AD. We also believe that it will improve cognition more than the control diet, particularly for those participants who do not carry an ApoE ε4 allele.

This pilot study will explore the feasibility and cognitive effects of a low carbohydrate, high fat, MAD in patients with MCI and early AD. If the results are promising, a larger-scale, multi-site clinical trial will be designed. The possibility that a safe, easy to implement, and inexpensive dietary intervention might improve the functioning of persons with MCI or early AD, or possibly even alter the course of dementia for some patients, might be a real “game-changer” in the field of AD therapeutics.

For more information contact:
Chandler J. Zolliecoffer, Johns Hopkins University School of Medicine
(P) 410-955-1647
czollie1@jhmi.edu
Deep Brain Stimulation of Fornix Shows Promise as Mild AD Treatment

BOSTON, Nov. 6, 2015 /PRNewswire/ -- Functional Neuromodulation Ltd. announced that an analysis of the ADvance Study, a Phase 2 double-blind randomized controlled trial of DBSf for mild Alzheimer's disease (clinicaltrials.gov NCT01608061) was presented at the 2015 Clinical Trials in Alzheimer's Disease (CTAD) meeting in Barcelona, Spain.

"The company is taking a unique approach to Alzheimer's disease by treating it as a disorder of the memory circuit that has become less active due to neuronal deterioration. By applying electrical impulses to the circuit, ADvance results suggest that DBSf may keep the memory circuit active," said Anton P. Porsteinsson, MD, William B. and Sheila Konar Professor of Psychiatry at the University of Rochester and a member of the independent data safety monitoring board for the ADvance study. Dr. Porsteinsson stated further, "The results are encouraging. The study demonstrated an acceptable safety and a suggestion of clinical benefit in a subgroup of patients, which is supported by improvement in a biological marker. This approach clearly merits further clinical investigation."

Treatment with DBSf suggested clinical benefit at 12 months in patients aged 65 and older based on Clinical Dementia Rating sum of boxes (CDR-SB) and the Alzheimer's Disease Assessment Scale cognitive subscale - 13 item, (ADAS-Cog 13). In patients treated with DBSf, glucose metabolism, a biomarker for neuronal degeneration and disease progression, increased by 22% on average at 12 months while the placebo group declined by 1.2% on average. The surgery and brain stimulation demonstrated acceptable safety and was well tolerated.

"DBSf has demonstrated a statistically significant increase in brain glucose metabolism and a signal that memory circuit activation may slow progressive cognitive changes in AD," said Vince Owens, CEO of Functional Neuromodulation. "Based on these results, we are advancing the DBSf clinical program to Phase 3 with plans to initiate enrollment in mid-2016."

ADvance Trial

ADvance is a randomized, double blind, controlled trial of 42 patients age 45 to 85 with mild Alzheimer's disease to evaluate the potential clinical benefit and safety of DBS of the fornix, a major inflow and output pathway in the brain's memory circuit. All patients were implanted with DBS systems and randomized to receive stimulation or sham stimulation for 12 months. The study was supported through a grant from the National Institute on Aging, part of the National Institutes of Health, awarded to Andres Lozano, MD, PhD, R.R. Tasker Chair in Stereotactic and Functional Neurosurgery at the University Health Network and University of Toronto and Constantine Lyketsos, MD, MHS, Elizabeth Plank Althouse Professor, Johns Hopkins University, and Director, Johns Hopkins Memory and Alzheimer's Treatment Center.

Continued on next page...
Rationale for DBS in Alzheimer's Disease

It is increasingly recognized that the pathological process in Alzheimer's disease causes focal synaptic dysfunction, the consequences of which produce widespread disturbances in the function of circuits and networks involved in cognition and memory. This notion is supported by the striking regional deficits in brain glucose utilization, impairments of the brain's default mode network, and aberrations in structural and functional brain connectivity characteristic of Alzheimer's disease. These disruptions are implicated in the pathogenesis of cognitive impairment. Thus malfunction in one diseased area interferes secondarily with other areas less affected but whose function is nevertheless disrupted because it is linked in the network. In contrast to recent therapeutic trials, a different approach is proposed: modulating the brain circuit dysfunction to improve function. As DBS has been used to modulate the activity of motor circuits in Parkinson's disease and other disorders it may be possible to use this same approach to modulate activity in dysfunctional cognitive neural circuits in Alzheimer's disease.

Clinical Results

The effect of DBS was measured using ADAS-cog-13, CDR-SB, and brain glucose metabolism as measured by FDG-PET with SPM analysis method. Increasing evidence exists that neuronal glucose metabolism is a main player in the complex processes involved with memory formation and retrieval. ADAS-cog-13 is used to assess a patient's cognitive status and CDR-SB assesses both cognitive and functional performance. The subgroup of interest in this analysis is ADvance patients aged 65 or older with mild AD. The subgroup includes 30 patients, with 15 in each arm. The ADvance trial was not powered to achieve statistical significance in clinical measures.

Continued on next page...
On glucose metabolism, patients in the DBSf treatment arm increased in five pre-specified brain regions of interest at 12 months whereas patients in the placebo group declined. Treated patients increased between 20.4% and 22.5% in the five regions, while the placebo group declined by 0.2% to 1.4%. This change was statistically significant at 6 months ($p = 0.03$), and the metabolism increase observed in the treatment group was maintained at 12 months.

On the ADAS Cog-13, patients in the placebo group worsened by an average of 7.8 at one year, whereas the worsening was 3.7 in the DBSf treatment arm. The trend toward slowing of clinical decline was not statistically significant ($p = 0.12$).

On the CDR-SB, patients in the placebo group worsened by an average of 3.5 at one year. In comparison, the worsening was 2.1 in the DBSf treatment arm. The trend toward slowing of clinical decline was not statistically significant ($p = 0.17$).

**Safety Results**

DBSf demonstrated an acceptable safety and tolerability profile in the ADvance study analysis, as previously reported. SAEs were consistent with what is typically observed in DBS of other study populations, including Parkinson's disease patients, the most common population treated with DBS.

**About Deep Brain Stimulation**

Deep brain stimulation (DBS) uses a surgically implanted medical device, similar to a cardiac pacemaker, to deliver mild electrical pulses to precisely targeted areas of the brain. The therapy is currently licensed in the United States, Europe, Canada and other regions of the world for the treatment of the disabling symptoms of essential tremor and advanced Parkinson's disease. It is available under a Humanitarian Device Exemption (HDE)¹ for primary dystonia in the United States. In Europe, Canada, Australia and Taiwan, DBS therapy is approved for the treatment of refractory epilepsy. The therapy is also approved for the treatment of severe, treatment-resistant obsessive-compulsive disorder in the European Union, Australia and in the United States under an HDE². More than 100,000 people worldwide have received DBS therapy.
An Alzheimer’s Clinical Trial Just for Caregivers

By Fran Kristz, California Health Report

Mallie Odle, 69, keeps a list on the refrigerator in the kitchen of her San Diego home of the things she enjoys doing in her rare spare time.

Recently she checked off lunch with a pal, and she has plans to make a bigger dent on that to-do list, including some exercise classes she hasn’t attended for a while.

A team of Alzheimer’s Disease researchers at the University of California/San Diego’s Department of Psychiatry is hoping for plenty of checkmarks on that list as well, but not because Odle has shown signs of the disease.

It's Odle’s husband, now 71, who has been diagnosed with Alzheimer's, and the UCSD department—which has been researching the impact of Alzheimer’s and other dementias on family caregivers for almost three decades—is hoping interventions can help prevent depression and cardiac disease in those caregivers.

“I thought it might help me cope with all of this better,” said Odle explaining why she joined the study a few months ago.

The critical need to help Alzheimer’s caregivers is increasing along with the incidence of the disease. Currently, 5.3 million Americans have Alzheimer’s or related dementia and that number is expected to double in the next ten years, according to the Alzheimer’s Association.

In California, 590,000 people currently have Alzheimer's disease and that number is expected to grow to 840,000 by 2025.

In San Diego, the number the number is currently 60,000, “more than in some entire states” says Jessica Empeno, director of family services and programs at the Alzheimer’s Association San Diego/Imperial chapter.

Research done through the UC San Diego Alzheimer’s Caregiver Study has linked serious health effects to Alzheimer’s and other dementia caregiving, including:

- Caregivers have stress levels that are four times higher than their non-caregiving peers.
- Caregivers are more than twelve times as likely to experience significant symptoms of depression.
- Caregivers report significantly lower confidence in their ability to cope effectively with life stresses compared to non-caregivers.
- Caregivers appear to have higher rates of hypertension and appear to be at higher risk of developing cardiovascular diseases. (Investigators found that compared to non-caregivers, caregivers have significantly higher blood concentrations of a biological marker believed to reflect the amount of atherosclerosis and vascular damage present in one’s body.)

Continued on next page...
Caregiver Study cont’d………

- Caregivers also appear to have higher blood concentrations of Interleukin-6 (IL-6), which increases coronary heart disease risk.
- The endothelium, which is the inner lining of blood vessels, appears to become less healthy the longer caregivers experience stress, which may lead to cardiovascular illness.

The clinical trial Mallie Odle and dozens of other Californians are enrolled in began a year ago and will run through 2019, funded by the National Institute on Aging, a division of the National Institutes of Health just outside Washington, D.C.

The goal is to evaluate the effectiveness of two educational programs to reduce stress, improve emotional well-being, and reduce risk for cardiovascular disease. The trial is open to caregivers who are 55 or older and provide in-home care for a loved one who has been diagnosed with Alzheimer’s disease or related dementia. Trial participants get up to five in-home health evaluations over the course of two years, including blood tests and an ultrasound scan of their cardiac arteries.

Trial participants are also divided into one of two intervention tracks: six at home sessions with a caseworker to learn how to better care for themselves physically and emotionally, or at home sessions where they get some support and printed information on caring for themselves.

The goal is to zero in on evidence-based practices that can be replicated by trained staff or even trained volunteers to help reduce the psychosocial and physical burden of caring for someone with Alzheimer’s or other forms of dementia.

The UCSD staff sees great promise in the efforts. Decades of research have shown that developing the right coping skills may benefit caregivers both emotionally and physically, says Brent Mausbach, PHD, an associate professor at UC San Diego and the study’s lead investigator.

“Earlier, smaller studies have shown that while increasing levels of stress seemed emotionally harmful in caregivers who felt least capable of coping well, stress had almost no impact on emotional health when caregivers felt confident in their coping skills,” says Mausbach. “More confident caregivers also appeared to have lower blood pressure and lower IL-6 compared to less confident caregivers.”

Mausbach says that research shows that nearly 40 percent of Alzheimer’s Disease family caregivers experience significant symptoms of clinical depression, compared to just five percent of older adults whose spouses are not ill.

“And because Alzheimer’s is a chronic disease, caregivers are in this role for a decade or longer,” he says.

One of the tracks being tested, support and information, is similar to what caregivers might already be getting through supports groups and one-day seminars in order to help them cope a bit better. The second track, the one Mallie Odle is a part of, is more structured and called “behavioral activation.”

Continued on next page......
Caregiver Study cont’d……

“We work with the caregiver to recognize that although they are doing a lot for their loved one they still have to take care of their own well-being,” says Mausbach. Often, he says, as Mallie Odle bears out, “they no longer socialize or engage in activities or hobbies they used to enjoy and we try to reactivate those parts of their lives.”

The study hopes to have 100 participants in each track, and recruiting is ongoing. (Eligible participants receive $500 in addition to the training.) Some participants, like Odle, have already completed the intervention part of the trial and will be followed for a full two years to assess changes—and whether they last. A smaller trial from 2008 to 2013 was successful in reducing depression symptoms in some participants “and gave us the proof of concept to begin the larger trial” says Mausbach.

And while improving the health of the caregivers is a key goal of the trial, there’s a much larger target also in mind.

“Ultimately if the caregiver doesn’t get help, that has implications for the healthcare system and insurers,” says Mausbach. “Now they have a condition that can be costly and if we can prevent that, it’s a positive win from a lot of stakeholders’ perspectives.”

Mausbach says Medicare data shown beneficiaries without Alzheimer’s cost the federal government an average of $2,000 in health costs each year compared to $13,000 for a beneficiary with dementia. Testing and honing the strategies also includes keeping the intervention costs low. “By putting less burden on agencies, we increase the chance they would want to offer the interventions,” says Mausbach.

Agencies in California, including nursing homes and long term care facilities, are showing interest in the concept. The Southern Caregiver Resource Center, based in San Diego, has tested the activation concept with Hispanic caregivers and is gathering data. One idea being considered by some agencies is to provide day care for the family member with Alzheimer’s or dementia during training for the caregiver to ensure that the caregiver will be able to attend the sessions.

Continued on next page…….
Mausbach said another idea to expand the option might be for caregivers to log their activity and emotional condition on line to let providers see how they are doing. Development of the technology is already underway and in testing by several social service agencies in San Diego. Mausbach says the UCSD team plans to publish interim analyses of factors in caregiving that are detrimental to health, and how to improve them, in the next year or two.

“What we want to know is who among caregivers is the stress most harmful to and how can we help them create coping mechanism to withstand the changes?” Possible outcomes waiting for verification include lower blood pressure readings when caregivers are more active.

Jessica Empeno, of the Alzheimer’s Association is excited about the research being done at UC/San Diego. “There is a lot of data out there that tells us the impact caring for a loved one has on a caregiver but some of it is a little dated and it’s always good to have the most up to date information,” Empeno says. But she adds that much more important than that are the different interventions the researchers are studying. “Having more evidence based information will help inform the practice of social workers and others in the field,” Empeno says.

However, Empeno says one challenge that will remain even once the UCSD study concludes is connecting caregivers with the information and resources. “Most think they are in this alone. They know they’re not sleeping or taking care of themselves, but they stop short of getting assistance, thinking” it’s not that bad, or it’s my duty or , I feel guilty taking care of myself when I should be taking care of my spouse.” Empeno says many even shy away from the term caregiver and says that too often caregivers put their own barriers in the way. “Hopefully having data that shows the impact will help, but there will still be some for whom it won’t have the intended effect,” says Empeno.

Late last year the San Diego County Board of Supervisors added urgency and funding in the efforts to help Alzheimer's patients and their families. Spurred by a conference she attended sponsored by the local Alzheimer’s Association chapter, Supervisor Diane Jacob championed the Alzheimer’s Project, now passed into law.

The Alzheimer’s Project brings together County and City of San Diego leaders; the County’s Health and Human Services Agency; researchers at UC San Diego, Scripps Research Institute, Sanford-Burnham Medical Research Institute and Salk Institute; Biocom; the San Diego County Medical Society; local law enforcement; the Alzheimer’s Association; caregivers and physicians. Among the components of the plan, which includes research funding, is expanded services and support for caregivers.

“Four out of five Alzheimer’s patients are cared for at home, and 85 percent of care is provided by family members or unpaid caregivers,” says County Supervisor Dave Roberts. “The disease...wears down families...”

But Mallie Odle may be a standard bearer for what research and intervention can do. This fall, based on advice from the UCSD clinical trial team, Odle added a day to her husband’s two day a week adult day care schedule, and now hopes to check even more activities she enjoys off that list on the fridge.
For information on the following studies please visit:

http://www.adcs.org/Studies/clinalResearchStudy.aspx

**NOBLE**

A Study for People with Mild to Moderate Alzheimer’s Disease

**A4** – Anti Amyloid in Asymptomatic Alzheimer’s Disease
More studies coming later in 2015 and 2016.....