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The Impact of a Cholesterol-Lowering Medication on Alzheimer's Disease

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the cholesterol-lowering medication ezetimibe and how it might disrupt protein interactions that lead to Alzheimer's disease and related dementia progression are Drs. Robert Reis and Srini Ayyadevara. Dr. Reis is a Professor and Researcher at the University of Arkansas for Medical Sciences' Institute on Aging College of Medicine and is a Research Career Scientist at the Central Arkansas Veterans Healthcare System's Geriatric Research, Education and Clinical, or GREC, Center.

Dr. Reis, it's a pleasure to have you with us.

Dr. Reis:
It's a pleasure to be here. Thank you.

Dr. Turck:
And Dr. Ayyadevara works alongside Dr. Reis as an Associate Professor at the UAMS Institute on Aging College of Medicine and is a Research Health Scientist at the Central Arkansas VA's GREC Center.

Dr. Ayyadevara, it's great to have you with us as well.

Dr. Ayyadevara:
Thank you for having me.

Dr. Turck:
So you both worked on a fascinating study that found that ezetimibe might reduce the risk of progression of Alzheimer's disease and related dementias. So starting with you, Dr. Reis, would you give us some background on your study?

Dr. Reis:
Certainly. We've been studying aging and age-dependent diseases for decades and Alzheimer's disease for just over a dozen years. We found that aggregates, conglomerations of sticky misfolded proteins, appeared in every mouse tissue we looked at, and we looked at brain, heart, kidney, skeletal muscle, and in several human tissues. We looked at human muscle biopsies through a collaboration, and also postmortem brain, and these all increased with age. But in addition to the age accrual of aggregates, brain, and especially the hippocampus, from Alzheimer's disease has disease-specific aggregates, called beta-amyloid and Tau tangles, so two different times named for the proteins first identified in them and thought to cede their initiation. That is to create the core around, which the aggregates form.

We worked out ways to isolate aggregates and purify each aggregate type, and then used mass spectrometry to identify the proteins inside them. Srinivas, working with Sundar Balasubramaniam in our group, then developed a new method to map the interior of aggregates to see which proteins connect to or contact which other proteins, and we found that Alzheimer's aggregates are not only much more abundant—about 60 percent more abundant—than aggregates from control brain or other tissues, but also are more interconnected. Their aggregate connectome is more complex. And this allowed us to identify especially important or influential protein-protein contacts, ones that stabilized aggregates and made them both larger and more enduring, more resistant to degradation.

This strategy revealed a key—I guess we call it a linchpin contact—between hexokinase-1, a mitochondrial membrane protein to one of a small family of 14-3-3 proteins, 14-3-3 G, or gamma. These proteins play a role in multiple signaling pathways. And this contact

occurs, surprisingly, both in A beta amyloid and in Tau tangle aggregates, and these are proteins that wouldn't normally interact at all as far as we know. So Sundaram targeted this interface, the place where hexokinase-1 adheres to 14-3-3 gamma, with thousands of drugs, so screening those drugs to find the ones that best stick and disrupt that sticky site, and that brings us up to the discovery of ezetimibe, which came out of that screening.

Dr. Turck:
So speaking of that, and turning to you, Dr. Ayyadevara, what was the objective of the study we're discussing? And who comprised the patient population?

Dr. Ayyadevara:
Yeah the study is basically to test, like Dr. Reis has mentioned, these 14-3-3 and hexokinase come together under conditions of AD, heart disease, and when we screen for an FDA-approved drug along with the small molecules, one of the top targets was ezetimibe. And also with the small molecule we tried to knock down 14-3-3 or the interaction that happens between these two proteins, 14-3-3 and hexokinase, and we found that in both in cells in culture and also in C ligands that are models of AD, they not only reduce protein aggregation and also this interaction but also improved the physiological function. Utilizing this primary data, we even mined the data, the pharma metrics plus database that spans from 2006 to 2020, and we looked at both heart disease patients and also at general population.

So in the data mining, we have found that the incidence of AD in the general population is 0.8 percent, but among the users of ezetimibe, it's 0.1 percent incidence. But as we have known, and per previous data, has actually shown that in traumatic brain injury, heart disease, they all elevate the incidence of AD.

In the coronary artery disease patients, the incidence of AD is 1.5 percent, almost twice that you normally find in general population, but the ezetimibe users actually had only 0.2 percent AD incidence, so that is a seven-fold reduction in the incidence of AD in the general population, and there's an eight-fold reduction in the incidence of AD among people who are using and also have coronary heart disease.

Dr. Turck:
Now, Dr. Reis, what are the mechanisms through which ezetimibe might reduce the harmful protein clumps that you described in the brain?

Dr. Reis:
Well, there are several possible mechanisms that could underlie this remarkable ability of ezetimibe to ward off Alzheimer's disease. The one we favor needn't be the only one, but it's the one that led us to ezetimibe in the first place, preventing or disrupting the interaction between hexokinase-1 and 14-3-3 gamma. But ezetimibe was FDA-approved and has been prescribed for over 22 years to lower cholesterol absorption. It's been displaced in the armamentarium of physicians by a succession of better and better statins. And statins were found to lower future Alzheimer's risk by up to 30 percent, probably by reducing plaque, but there's no certainty as to the exact mechanism, so cholesterol reduction is also a likely mechanism to explain part of ezetimibe's efficacy in preventing Alzheimer's.

We also showed that ezetimibe restores autophagy, which otherwise declines markedly as we age. Autophagy is the cell's garbage truck tasked with disposing of fairly large aggregates and also defunct mitochondria, etc., so the 50 percent boost with ezetimibe in autophagy efficacy is biologically important. This rescue might be expected in view of the presence of 14-3-3 in aggregates since 14-3-3 proteins modulate autophagy. They don't always enhance it. In some cases, they reduce it. But they definitely affect autophagy, so attenuation of autophagy is the third mechanism. And for all we know, there may be additional mechanisms that have yet to be discovered.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Robert Reis and Srini Ayyadevara about their research on the cholesterol-lowering medication ezetimibe and how it might target some of the keys to the progression of Alzheimer's disease and related dementias.

So now that we have some background on your study, let's dive into the findings. Dr. Ayyadevara, would you walk us through some of the key results?

Dr. Ayyadevara:
Yeah. Actually, as Dr. Reis mentioned, protein aggregation increases not only in AD but also in heart disease. And among these proteins, the key influential interactions that actually happen during AD and also heart disease is between hexokinase and 14-3-3 gamma. And we screened these FDA-approved drugs to see if there are any that actually bind this interaction and prevent these two interactions that actually happen during a disease—and prevent of disease progression—and we found ezetimibe that came out in the

initial screening, so our goal is to see if ezetimibe can prevent this interaction and also improve physiological functions.

And after testing in cells in culture and C inhibitor model C ligands, which it improved the function and also reduced protein aggregation, we mined the clinical databases, and that also supported the property of ezetimibe, as well as AD, to 0.14 overall among the general population and greater than 0.12 person in higher-risk heart disease patients. And so we are encouraged by that, and we are—even though it's a retrospective study—we are gearing up to do prospective studies to see if it helps even in other populations.

Dr. Turck:
And, Dr. Reis, how do you think ezetimibe compares to other drugs that we presently use to treat Alzheimer's disease?

Dr. Reis:
Well, for efficacy it's head and shoulders above any of the others with 7- to 8-fold improvement in respective incidents of Alzheimer's being diminished by 7- to 8-fold. The other classes of drugs that are prescribed at the present for Alzheimer's and related dementias are cholinesterase inhibitors, which tend to help about 1 out of 10 patients but also produce unpleasant side effects in about 1 out of 10 patients. Then there are the glutamate blockers or NMDA receptor antagonists, like memantine which show no benefit for progression but symptom, symptomatic relief. The most recent additions to our armamentarium have been monoclonal antibodies to A beta. Aducanumab and lecanemab were given fast-track FDA approval. Donanemab is still going through clinical trials. And they all slow cognitive decline and PET scan incidence of amyloid plaque in the brain by about 20–30 percent, but they are accompanied by brain swelling and bleeding and impaired vision in a reasonable fraction of patients so that those are concerns that have to be weighed against the benefits.

Ezetimibe, on the other hand, causes only rare and minor side effects, such as muscle aches and pains, indigestion, sore throat, runny nose, sneezing and occasional dizziness. We also had a couple of other drugs that were about equally effective in disrupting the hexokinase-14-3-3 interface. Those were conivaptan and lumacaftor, but they were not as well tolerated as ezetimibe, so we didn't pursue those. We're basically considering ourselves very lucky to have found a drug as benign as ezetimibe that few would have hesitancy in prescribing in a preventative role and has yet to be tested in blind clinical trials for efficacy for this particular condition for prevention of progression into Alzheimer's and related dementias; but we have proposed studies to do that, and we hope to have a definitive answer so it could even be prescribed for this indication. As of right now, it would be prescribed off label.

Dr. Turck:
And lastly, Dr. Ayyadevara, you started to go into this just a little bit, but what would you say are the next steps for further fleshing out the potential role of ezetimibe in the progression of Alzheimer's disease and related dementias?

Dr. Ayyadevara:
There are numerous factors, actually, that predispose the progression of mild cognitive impairment or dementia and Alzheimer's disease, and some of the factors that include not only heart disease but traumatic brain injury, and APOE 4 allele for that matter also elevates the risk of Alzheimer's disease. So, like I said, the retrospective study is encouraging, but we should do some prospective studies on MCI heart disease patients to see if the conversion to Alzheimer's is lower, because as in the initial preliminary studies, we have seen that there is a 2-fold increase in the incidence of Alzheimer's disease among card—cardiac patients. And we all know that APOE 4 allele and also traumatic brain injury also elevates the incidence of AD, so we wanted to test if the conversion of MCI and TBI into AD is lowered by using ezetimibe. Part of the thing is to prevent the occurrence of AD, and we can also treat AD patients with ezetimibe to see if it actually can help in reversing the disease.

Dr. Turck:
That's a great look ahead as we come to the end of today's program, and I want to thank my guests, Drs. Robert Reis and Srini Ayyadevara, for joining me to discuss the potential role of ezetimibe in reducing the progression of Alzheimer's disease and related dementias. Dr. Reis, Dr. Ayyadevara, it was great having you both on the program.

Dr. Reis:
Thank you so much for inviting us.

Dr. Ayyadevara:
Thank you again for inviting us.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.