Science Translational Medicine Podcast

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Host – Orla Smith
Hello, I'm Orla Smith. Welcome to the *Science Translational Medicine* Podcast for May 14th 2014. In this show, I will be speaking with Dr. Yvette Sheline from the University of Pennsylvania in Philadelphia. Her new study shows that an antidepressant drug reduces amyloid-beta in the mouse and human brain. Amyloid-beta accumulation in the brain is a key pathological hallmark of Alzheimer's disease. It is believed that one way to stave off Alzheimer's disease may be to reduce amyloid-beta in the brain during the early stages of disease before it aggregates into clumps and brain neurons start to die off.

Here now is Dr. Sheline on the line to tell us more.

Interviewer – Orla Smith
Welcome, Dr. Sheline, and thanks for joining us.

Interviewee – Yvette Sheline
Thank you. Welcome.

Interviewer – Orla Smith
So how big a problem is Alzheimer's disease?

Interviewee – Yvette Sheline
Alzheimer's disease is the single most common form of dementia. So it's prevalent, right now, in about five million adults in the U.S. alone and worldwide in a much, much higher number of patients. So it's probably the single most important issue facing us—both medically and economically—because these patients, as they get demented, require a huge amount of care both hospital and end-of-life care.

Interviewer – Orla Smith
And what treatment options are currently available?

Interviewee – Yvette Sheline
Right now there is no curative option for Alzheimer's disease. There are several drugs that are under development and others that are in clinical trials. But at this point in time, there is no treatment that can cure Alzheimer's disease.

Interviewer – Orla Smith
So turning to your study, why did you choose an antidepressant drug?

Interviewee – Yvette Sheline
In this most recent study, basically, based on our earlier study, which we published in *PNAS* 2 years ago, what we had found in that study was that the SSRI, selective serotonin reuptake inhibitor, class of drugs reduced in a mouse model of amyloid the levels of amyloid-beta.

Interviewer – Orla Smith
Tell us about your mouse model.

Interviewee – Yvette Sheline
We used an aged transgenic Alzheimer's disease mouse model, the APP/PS1 plaque-bearing mice, so we studied them after they have plaques in their brain, which then it mimics the human Alzheimer's model of dementia. And in these mice, what we did was give them several different doses of the SSRI citalopram, which is one particular SSRI, and showed that there was a dose-dependent reduction in the concentrations of amyloid-beta in the mouse interstitial fluid.

Interviewer – Orla Smith
So what is brain interstitial fluid?

Interviewee – Yvette Sheline
It's the equivalent of human cerebrospinal fluid so it bathes the hippocampus and would be where you would observe—just like in human cerebrospinal fluid—it would be the place where you would observe changes in amyloid as there was a greater or lesser production of amyloid.

Interviewer – Orla Smith
And what did you find in your mice?

Interviewee – Yvette Sheline
Well, we found two different things. One was a dose-dependent reduction in amyloid-beta. So in other words, the more SSRI you had the lower the amyloid concentration suggesting that it was the SSRI that produced the reduction in the amyloid-beta concentration. And the other effect—in a mouse model that had had thin-skull surgery to synapse the skull so that we could observe through two-photon microscopy—we found that as individual plaques were visualized and followed over a month the plaques in mice that received citalopram had no growth, they stayed static, they were sort of arrested at the current growth stage; and there were no new plaques that were formed. However, in mice that got vehicle, you know, sugar water, they continued to grow plaques at the usual rate. So that's another piece of evidence from the mouse models, as well.

Interviewer – Orla Smith
You also looked in the cerebrospinal fluid of healthy human volunteers, right?

Interviewee – Yvette Sheline
What we did in the humans was we used young, healthy people between the ages of 20 and 45, and in in those people we put a spinal catheter—like what you would get for a lumbar puncture, except that in this case it was an indwelling catheter—so that we could sample spinal fluid every hour for 36 hours so that we could see what happened to the levels of amyloid-beta. At the same time, prior to putting in this catheter, we had given them a fairly large dose of citalopram and then started sampling in the morning—so we gave them the dose of antidepressant at midnight and then started examining the spinal fluid in the morning to give enough time for the effect to occur—and then we followed every hour over the next 36 hours to see what happened to the concentrations of amyloid. In addition, we gave them a dose of leucine, which is an amino acid, that had been labeled with carbon-13. Now this is not radioactive, but what it is a different isotope of the carbon so that it could be detected in the mass spectrometer, and we could see how much of this new leucine was incorporated into this protein and how much had the usual carbon-12 and therefore was old, not newly synthesized. So we could look not only at the newly synthesized amyloid but also at the amyloid concentrations.

Interviewer – Orla Smith
And what did you find?

Interviewee – Yvette Sheline
So we found that both the newly synthesized amyloid was slowed, and the concentrations were decreased. So I think looking at this here it was a 37% slowing in the citalopram group compared to the placebo group and a 38% decrease in the total CSF Abeta concentrations in the drug-treated group.

Interviewer – Orla Smith
And how does this antidepressant reduce amyloid-beta in the human brain?

Interviewee – Yvette Sheline
There are a number of experiments going on in the lab of my colleague, John Cirrito, and it appears to be through what are called the GS protein receptor binding sites, which then go on and make changes in a extracellular receptor kinase, ERK. So he's done experiments where he's done blocking of ERK to show that if you do that then you cannot get this effect. So the experiments to show exactly what the pathways are that are involved are still ongoing. But it appears that there are specific serotonin receptor subtypes that are responsible for this and that they activate ERK activity so that the ERK then potentially goes on and lowers secretase activity.

Interviewer – Orla Smith
And how long will it be before antidepressants like citalopram can be tested in patients with Alzheimer’s disease?

Interviewee – Yvette Sheline
Well, I don't think we will ever be interested in testing them in Alzheimer's disease because we don't believe this would have any effect in Alzheimer's disease once that

disease has already gotten going in the brain and started to kill off neurons and make people demented. But what we would like to see is for this to be developed as a prophylactic preventive measure so that perhaps in initially in people who were high risk or perhaps—since it's a fairly safe treatment—perhaps in a in a larger group of people so that they would never get to the point of having Alzheimer's disease; or if they did get Alzheimer's disease it would be slowed by many, many years. That would be our goal.

Interviewer – Orla Smith
Are there any preventive trials currently planned?

Interviewee – Yvette Sheline
The next step we're going to take is we're going to move this protocol to older people, healthy older people, and show that when we give several weeks of SSRI treatment that they have a lowering of amyloid-beta. So those trials are just starting. And if that's effective and we show that this works in older folks and decreases the amyloid burden that they have, then we would be ready to start a biomarker trial where we show that we can lower the amyloid burden in CSF over a period of years perhaps to show that that really made a difference. So that's a longer-term goal.

Interviewer – Orla Smith
Dr. Sheline, thank you so much for joining us today and congratulations on a very interesting paper.

Interviewee – Yvette Sheline
Thank you.

Host – Orla Smith
That was Yvette Sheline from the University of Pennsylvania in Philadelphia. Check out her *Science Translational Medicine* paper online by going to our Web site at stm.sciencemag.org.

I'm Orla Smith, thanks for listening!

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