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PBA Treatment May Reverse Signs of Alzheimer's Disease

**Dr. Wilner:**
A new preclinical study published in the journal *Aging Biology* focused on the impacts of a compound called 4-phenylbutyrate, or PBA for short, on memory impairment in a mouse model of Alzheimer's disease. So what are the findings and the implications for the more than six million Americans living with Alzheimer's disease?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner. And joining me today is Dr. Jini Naidoo, the study's lead author. Dr. Naidoo is a Research Associate Professor of Sleep Medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Dr. Naidoo, it's great to have you with us today.

**Dr. Naidoo:**
Great to be here, Dr. Wilner.

**Dr. Wilner:**
Let's start with some background. I'm not familiar with PBA treatment. What prompted you to investigate PBA's effect on Alzheimer's disease?

**Dr. Naidoo:**
PBA, or 4-phenylbutyrate, is a small saturated fatty acid that acts as a chaperone. And by "chaperone," I mean this is a molecule or a protein that helps newly synthesized proteins to fold or to help misfolded proteins refold. So essentially, it's a molecule or a protein that prevents proteins from aggregating. And as we know, in neurodegenerative diseases, protein aggregation is a major problem.

So we first started to use PBA to improve sleep quality in aged fruit flies and then later used it to improve sleep and to reverse cognitive decline in aged mice. So part of our rationale for using PBA was that we noticed that a key endogenous chaperone important for maintaining protein homeostasis, and by that I mean the way proteins get made, folded, transported, and degraded in the cell, this particular chaperone, which occurs in an organelle called the endoplasmic reticulum, actually declined with age. So we asked if this key chaperone declines with age, and since it's often found associated with a lot of protein aggregation when you have reductions in this protein, can we supplement the levels of the chaperone with a small molecule that acts in a manner that's very similar to it and something that would help promote protein homeostasis and maintain cellular health.

**Dr. Wilner:**
What I remember from medical school is that proteins have a three-dimensional shape, and they're folding is critical because even if you have all the same amino acids but they're not folded correctly, then they won't work. So I didn't know that they had a chaperone to help. That sounds pretty cool.

**Dr. Naidoo:**
There are many, many chaperones that help with protein folding, but this particular chaperone that we study in our lab is called BiP or HSPA5. It's really critical for several things, including protein folding. It is also a calcium-binding protein, so it helps maintain calcium homeostasis in the cell. It has a host of functions. And so what we found, quite by accident, was that in aged mice and in aged fly brains, this protein declines with age, and so we thought if it's that important, it must impact several processes.

**Dr. Wilner:**
So with that background in mind, how did you set up the experiment?

**Dr. Naidoo:**

Our major objective for this particular experiment using a model of Alzheimer's disease was to determine whether we could reduce cellular stress or protein dyshomeostasis. So with all neurodegenerative diseases, whether it's Parkinson's or Alzheimer's or ALS, one of the key factors is you see a lot of protein aggregation and you have a lot of cellular dysfunction. And so the other thing about Alzheimer's disease is you get runaway production of amyloid, which tends to form these plaques, so we wanted to know if we could mitigate some of the effects of the disease—the protein aggregation and dyshomeostasis—just by reducing that level of cellular stress. We thought PBA would be a good candidate to help do that.

The other important thing about Alzheimer's disease is one of the first symptoms of Alzheimer's disease is cognitive impairment, and so we wanted to know whether we could delay or, in fact, reverse some of that cognitive decline that's found in the disease. Another factor that we wanted to look at is the effect of cellular stress on pathology, so can we again mitigate some of those pathological changes in this mouse model that we chose to use, and the one we used was one called an App knock-in mouse, meaning that this mouse would in time make more Aβ42, which is the toxic form of Aβ.

**Dr. Wilner:**
So you got a bunch of mice that got PBA and a bunch of mice didn't get PBA?

**Dr. Naidoo:**
Yes. The way we formulated the study is first, we didn't know exactly when the drug would work best, so we took newborn mice directly from weaning and we treated them with PBA. A group of mice got PBA, and another group of very young mice got a vehicle—saline, in fact. We fed them both these drugs as well as gave them some injections once a week, and we did this for 10 weeks and then tested these mice in a spatial recognition test, a spatial learning test. So this memory test requires use of a part of the brain called the hippocampus. It's hippocampal-dependent learning. Basically, you train the mice with two objects in an arena. Then you'd remove them from the arena and move one of the objects. Mice are naturally curious animals, and so they'll tend to interact with the moved object or the novel object, and if the mice had learned the original location, when you reintroduce them to the arena, they would then interact with the moved object because that is the novel environment now. And so what we did was we tested these mice after 10 weeks of PBA treatment and found that the young mice that were treated with PBA performed just the same as wild-type mice, so these are the Alzheimer's mice performing as well as wild-type mice when the mice that are saline-treated actually fail the test.

The question is that often cognitive decline occurs well after pathological changes have taken place, and how does one treat people who already have cognitive impairment? Because we had taken very young mice and it takes a while for cognitive impairment to actually occur in the disease, we thought let's start a second cohort of mice at a much later stage. So we started them around 12 months old when we knew they would be a lot more debilitated in that they would have the cognitive impairment; they would have pathological changes; and we started the treatment at around 12 months old for 10 weeks and then tested those mice. And to our surprise, pleasant surprise I would say, we found that the Alzheimer's mice treated with the PBA that we started later on actually performed as well as the mice that were wild-type.

**Dr. Wilner:**
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Jini Naidoo about her research on how a compound called PBA may mitigate or slow the progression of Alzheimer's disease.

So, what happens now?

**Dr. Naidoo:**
PBA has not been tested clinically for Alzheimer's disease, so it hasn't been used in any clinical trial, so that would probably be the next step. But we know that PBA is an FDA-approved drug. It's being used for other disorders. It's a drug that has been used for several decades for urea cycle disorders, and it's only just recently been approved to be used in combination with another small molecule for the treatment of ALS. I think there's potential for this drug or at least for the small molecule to help improve cellular health and thereby probably mitigate some of the aspects of Alzheimer's disease.

**Dr. Wilner:**
Before we close, Dr. Naidoo, do you have any final takeaways you'd like to leave with our audience today?

**Dr. Naidoo:**
We began working with PBA because of our interest in the relationship between protein homeostasis and sleep. Our work had shown that sleep disruption and chronic sleep loss actually perturbs protein homeostasis, and it's becoming increasingly known that chronic sleep loss leads to neuronal injury and may actually be a contributing factor to Alzheimer's disease. So I think one of the things that people could actually do is to pay attention to one's sleep.

**Dr. Wilner:**

With those final comments in mind, I want to thank my guest, Dr. Jini Naidoo, for joining me on *NeuroFrontiers* to share the results of this exciting Alzheimer's disease research. Dr. Naidoo, it was a pleasure having you on the program today.

**Dr. Naidoo:**
Thank you, Dr. Wilner.

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