MedicalXpress

FDA-approved drug rapidly clears amyloid from the brain, reverses Alzheimer's symptoms in mice

February 9 2012

Neuroscientists at Case Western Reserve University School of Medicine have made a dramatic breakthrough in their efforts to find a cure for Alzheimer's disease. The researchers' findings, published in the journal *Science*, show that use of a drug in mice appears to quickly reverse the pathological, cognitive and memory deficits caused by the onset of Alzheimer's. The results point to the significant potential that the medication, bexarotene, has to help the roughly 5.4 million Americans suffering from the progressive brain disease.

Bexarotene has been approved for the treatment of cancer by the U.S. Food and Drug Administration for more than a decade. These experiments explored whether the medication might also be used to help patients with Alzheimer's disease, and the results were more than promising.

Alzheimer's disease arises in large part from the body's inability to clear naturally-occurring amyloid beta from the brain. In 2008 Case Western Reserve researcher Gary Landreth, PhD, professor of neurosciences, discovered that the main cholesterol carrier in the brain, Apolipoprotein E (ApoE), facilitated the clearance of the amyloid beta proteins. Landreth, a professor of neurosciences in the university's medical school, is the senior author of this study as well.

Landreth and his colleagues chose to explore the effectiveness of

bexarotene for increasing ApoE expression. The elevation of brain ApoE levels, in turn, speeds the clearance of amyloid beta from the brain. Bexarotene acts by stimulating retinoid X receptors (RXR), which control how much ApoE is produced.

In particular, the researchers were struck by the speed with which bexarotene improved memory deficits and behavior even as it also acted to reverse the pathology of Alzheimer's disease. The present view of the scientific community is that small soluble forms of amyloid beta cause the memory impairments seen in animal models and humans with the disease. Within six hours of administering bexarotene, however, soluble amyloid levels fell by 25 percent; even more impressive, the effect lasted as long as three days. Finally, this shift was correlated with rapid improvement in a broad range of behaviors in three different mouse models of Alzheimer's.

One example of the improved behaviors involved the typical nesting instinct of the mice. When Alzheimer's-diseased mice encountered material suited for nesting – in this case, tissue paper – they did nothing to create a space to nest. This reaction demonstrated that they had lost the ability to associate the tissue paper with the opportunity to nest. Just 72 hours after the bexarotene treatment, however, the mice began to use the paper to make nests. Administration of the drug also improved the ability of the mice to sense and respond to odors.

Bexarotene treatment also worked quickly to stimulate the removal of amyloid plaques from the brain. The plaques are compacted aggregates of amyloid that form in the brain and are the pathological hallmark of Alzheimer's disease. Researchers found that more than half of the plaques had been cleared within 72 hours. Ultimately, the reduction totaled 75 percent. It appears that the bexarotene reprogrammed the brain's immune cells to "eat" or phagocytose the amyloid deposits. This observation demonstrated that the drug addresses the amount of both

soluble and deposited forms of amyloid beta within the brain and reverses the pathological features of the disease in mice.

This study identifies a link between the primary genetic risk factor for Alzheimer's disease and a potential therapy to address it. Humans have three forms of ApoE: ApoE2, ApoE3, and ApoE4. Possession of the ApoE4 gene greatly increases the likelihood of developing Alzheimer's disease. Previously, the Landreth laboratory had shown that this form of ApoE was impaired in its ability of clear amyloid. The new work suggests that elevation of ApoE levels in the brain may be an effective therapeutic strategy to clear the forms of amyloid associated with impaired memory and cognition.

"This is an unprecedented finding," says Paige Cramer, PhD candidate at Case Western Reserve School of Medicine and first author of the study. "Previously, the best existing treatment for Alzheimer's disease in mice required several months to reduce plaque in the brain."

Added Professor Landreth: "This is a particularly exciting and rewarding study because of the new science we have discovered and the potential promise of a therapy for Alzheimer's disease. We need to be clear; the drug works quite well in mouse models of the disease. Our next objective is to ascertain if it acts similarly in humans. We are at an early stage in translating this basic science discovery into a treatment."

Daniel Wesson, PhD, assistant professor of neurosciences at Case Western Reserve School of Medicine and co-author of the study agreed.

"Many often think of Alzheimer's as a problem of remembering and learning, but the prevalent reality is this disease spreads throughout the brain, resulting in serious insults to numerous functions," he said. "The results of this study, showing the preservation of behaviors across a wide spectrum, and accompanying brain function, are tremendously exciting

and suggest great promise in the utility of this approach in treatment of Alzheimer's disease."

Bexarotene has a good safety and side-effect profile. The Case Western Reserve researchers hope these attributes will help speed the transition to clinical trials of the drug.

Professor Landreth said modest resources funded this self-described "far-fetched idea." Crucial support came from the Blanchette Hooker Rockefeller Foundation, the Thome Foundation, and the National Institutes of Health.

Provided by Case Western Reserve University