Targeting the blood-brain barrier may delay progression of Alzheimer's disease

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Researchers may be one step closer to slowing the onset and progression of Alzheimer's disease. An animal study supported by the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health, shows that by targeting the blood-brain barrier, researchers are able to slow the accumulation of a protein associated with the progression of the illness. The blood-brain barrier separates the brain from circulating blood, and it protects the brain by removing toxic metabolites and proteins formed in the brain and preventing entry of toxic chemicals from the blood.

"This study may provide the experimental basis for new strategies that can be used to treat Alzheimer's patients," said David S. Miller, Ph.D., chief of the Laboratory of Toxicology and Pharmacology at NIEHS and an author on the paper that appears in the May issue of *Molecular Pharmacology*.

Alzheimer's is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually disrupts function of major organs. Estimates vary, but experts suggest that as many as 2.6 million to 5.1 million Americans may have Alzheimer's. One hallmark of Alzheimer's is the deposition of beta-amyloid protein in the brain. This protein clumps to form plaques that destroy neurons and lead to cognitive impairment and memory loss in Alzheimer patients.

"What we've shown in our mouse models is that we can reduce the accumulation of beta-amyloid protein in the brain by targeting a certain receptor in the brain known as the pregnane X receptor, or PXR," said Miller.

The researchers from NIEHS and the University of Minnesota Duluth demonstrated that when 12-week-old genetically modified mice expressing human beta-amyloid protein are treated with a steroid-like chemical that activates PXR, the amount of beta-amyloid protein in the brain is reduced. The activation of the PXR was found to increase the expression of a blood-brain barrier protein known as P-glycoprotein. This protein transports beta-amyloid out of the brain.

"Our results show several new findings. We now know that P-glycoprotein plays a pivotal role in clearing beta-amyloid from the brain. Secondly, we know P-glycoprotein levels are reduced in the blood-brain barrier, and that the Alzheimer's mice treated with the chemical to activate PXR were able to reduce their beta-amyloid levels to that of mice without Alzheimer's," said Bjorn Bauer, Ph.D., assistant professor at the University of Minnesota and senior author on the paper.

Anika Hartz, Ph.D., lead author on the study, added that it is also likely that reduced P-glycoprotein expression at the blood-brain barrier may be an early indicator of Alzheimer's disease, even before the cognitive symptoms appear. One of the challenges confronting the diagnosis and treatment of Alzheimer's is being able to clearly diagnose the disease process when brain damage is minimal, before any symptoms occur.

"More research is needed before this animal model discovery can be tested in humans, but the paper suggests some new targets for treatment that offer hope to patients and families dealing with this devastating disease," said NIEHS Director Linda Birnbaum, Ph.D.

The researchers plan to conduct a study where the Alzheimer's mice are fed a PXR-activating compound in their diet for 12-18 months. The cognitive skills of the animals will be monitored regularly, along with their P-glycoprotein levels, to determine whether the feeding regimen delays the onset of cognitive impairment.

More information: Hartz AM, Miller DS, Bauer, B. 2010. Restoring Blood-Brain Barrier P-glycoprotein

Reduces Brain Abeta in a Mouse Model of Alzheimer's Disease. Mol Pharmacol. Online January 25, 2010. doi:10.1124/mol.109.061754

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