Can a protein controlling blood pressure enhance immune responses and prevent Alzheimer's?

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Many people with high blood pressure are familiar with ACE inhibitors, drugs that widen blood vessels by limiting activity of ACE – angiotensin-converting enzyme – a naturally occurring protein found in tissues throughout the body.

But high activity of the enzyme – in the right context, place and time – may be a good thing. A study conducted by Cedars-Sinai scientists found that genetically targeting certain immune blood cells to overproduce the enzyme broke down defective proteins in the brain associated with Alzheimer's disease and prevented cognitive decline in laboratory mice bred to model the disease.

The study, to be published in the March issue of the *Journal of Clinical Investigation*, demonstrates for the first time that ACE, which is largely known for its effects outside the central nervous system, can, in fact, induce a protective immune response in the brain and affect cognition. Moreover, it identifies a novel role for ACE in the clearance of beta-amyloid in brain blood vessels.

Kenneth Bernstein, MD, professor of biomedical sciences and professor of pathology and laboratory medicine, is a lead author of the article with Yosef Koronyo, MSc, research associate in the Department of Neurosurgery. Bernstein, director of experimental pathology and a research scientist in the Department of Biomedical Sciences, engineered

study mice to overexpress ACE in macrophages, microglia and similar cells of the immune system. Other researchers in these departments contributed to the article.

"Our study shows the value of a combination strategy that delivers an enzyme to attack and destroy beta-amyloid protein in the brain and enhances the immune system's ability to clear beta-amyloid and resist other brain-damaging processes like uncontrolled inflammation," said Maya Koronyo-Hamaoui, PhD, assistant professor of neurosurgery in the Department of Neurosurgery and the Department of Biomedical Sciences. A research scientist at the Maxine Dunitz Neurosurgical Institute, Koronyo-Hamaoui is the article's senior and corresponding author.

Accumulation of beta-amyloid protein in the brain is strongly associated with Alzheimer's disease. Protein levels and plaque deposits build up slowly, damaging and destroying brain cells and setting up an inflammatory process that generally is believed to add to the gradual but unrelenting decline of mental function. Scientists have not determined if the deposits result from an overproduction of beta-amyloid protein or from an inability of mechanisms, such as the immune system, to adequately clear it. In either case, a common view is that any strategy that reduces the amount of beta-amyloid protein in the brain early in disease development is highly likely to help prevent disease progression.

In this study, mice genetically engineered to have Alzheimer's-like plaques and symptoms were bred with mice engineered to overexpress ACE in immune cells in the blood. The offspring of the two strains had greatly reduced beta-amyloid protein levels and inflammation and their performance on learning and memory tests was similar to that of normal mice.

The study spotlights ACE as a naturally occurring enzyme that can have

either detrimental or beneficial effects, depending on how and where it is active. It contributes to production of angiotensin II, a hormone that often causes blood vessels to narrow and blood pressure to rise; inhibiting the enzyme relaxes vessels and reduces pressure. But in the brain, high levels of ACE quickly and efficiently led an immune system response against beta-amyloid protein.

"We were absolutely astonished by the lack of Alzheimer's-associated pathology in the crossed mice at the age of 7 months and again at a 13-month follow-up. At first, we thought we had a genotyping error in identifying these mice as carriers of the aggressive familial Alzheimer's mutations. But we verified their genotypes and ran the experiments again and again and confirmed the same findings. Even more importantly, this strategy resulted in a near-complete prevention of the cognitive decline in this mouse model of Alzheimer's disease," Koronyo-Hamaoui said. "Later, by using ACE inhibitors, we were able to confirm that the interruption of disease progression was dependent on ACE function and the chemical reactions it brought about, which provided us with great insights into the mechanism by which these benefits were obtained in the mouse models."

Microglia are immune cells in the brain responsible for protecting the organ from foreign bodies and clearing away dying cells, but they become inefficient in controlling the toxic beta-amyloid proteins in Alzheimer's disease. Similar immune cells in the blood have proved more capable. Earlier studies found that when bloodborne immune cells called monocytes were "recruited" into the brain, the cells readily homed to plaques and assisted in clearing them. Koronyo-Hamaoui has studied the role of immune system cells in Alzheimer's disease for the last decade.

Previous studies showed that ACE overexpression could elevate immune responses against tumors and bacterial infections. This study extends the

findings to Alzheimer's.

The authors said in the article that "while it is possible to envision a strategy for delivering ACE-overexpressing monocytes to patients, perhaps the most informative finding of our studies is the effectiveness of combining an approach to enhance the immune response with that of delivering inflammatory cells to enzymatically destroy beta-amyloid."

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More information: *Journal of Clinical Investigation*: "Angiotensin converting enzyme overexpression in myelomonocytes prevents Alzheimer's-like cognitive decline."

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