Damaged blood vessels loaded with amyloid worsen cognitive impairment in Alzheimer's disease

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A team of researchers at Weill Cornell Medical College has discovered that amyloid peptides are harmful to the blood vessels that supply the brain with blood in Alzheimer's disease—thus accelerating cognitive decline by limiting oxygen-rich blood and nutrients. In their animal studies, the investigators reveal how amyloid-β accumulates in blood vessels and how such accumulation and damage might be ultimately prevented.

Their study, published in the Feb. 4 online edition of the Proceedings of the National Academy of Sciences (*PNAS*), is the first to identify the role that the innate immunity receptor CD36 plays in damaging cerebral blood vessels and promoting the accumulation of amyloid deposits in these vessels, a condition known as cerebral amyloid angiopathy (CAA).

Importantly, the study provides the rational bases for targeting CD36 to slow or reverse some of the cognitive deficits in Alzheimer's disease by preventing CAA.

"Our findings strongly suggest that amyloid, in addition to damaging neurons, also threatens the cerebral blood supply and increases the brain 's susceptibility to damage through oxygen deprivation," says the study's senior investigator, Dr. Costantino Iadecola, the Anne Parrish Titzell Professor of Neurology at Weill Cornell Medical College and director of the Brain and Mind Research Institute at Weill Cornell Medical College

and NewYork-Presbyterian Hospital. "If we can stop accumulation of amyloid in these blood vessels, we might be able to significantly improve cognitive function in Alzheimer's disease patients. Furthermore, we might be able to improve the effectiveness of amyloid immunotherapy, which is in clinical trials but has been hampered by the accumulation of amyloid in cerebral blood vessels."

Mounting scientific evidence shows that changes in the structure and function of cerebral blood vessels contribute to brain dysfunction underlying Alzheimer's disease, but no one has truly understood how this happens until now.

In the study, the research team—which also includes investigators from the Mayo Clinic in Florida, the McLaughlin Research Institute in Montana and The Rockefeller University—used mice that were genetically modified to develop amyloid in their brain and blood vessels, but in which the CD36 receptor was eliminated. They demonstrated that mice lacking CD36 have less buildup of amyloid in cerebral arteries (CAA) even if they have massive amyloid buildup in their brain tissue (amyloid plaques).

"Remarkably, mice lacking CD36, in which only CAA is reduced, perform significantly better in cognitive tests than do mice with intact CD36," says the study's first author, Dr. Laibaik Park, an assistant professor of neuroscience in the Brain and Mind Research Institute.

"In essence, reduced amyloid burden in cerebral blood vessels, or CAA, was able to preserve cognitive function despite the buildup of amyloid plaques in the brain tissue," says Dr. Iadecola, who is also a neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. "These findings indicate that clearing the amyloid from cerebral blood vessels might be of tremendous benefit to patients with Alzheimer's disease. These conclusions are based on mice studies, and mice are not

humans, of course, but we have a very exciting new direction to explore in our search for Alzheimer's disease therapies."

Scavenger Molecule Response Damages Blood Vessels

CAA is already known to be a major cause of brain dysfunction and hemorrhage from weak, damaged brain arteries in some elderly patients, but no one has identified how it occurs. It is also not clear how many older adults suffer from CAA because there is no way to make a clear diagnosis of the condition, unless sophisticated brain imaging studies are performed. But it is believed that this condition is widespread and that CAA, either in association with Alzheimer's disease or independent of it, is a major cause of cognitive decline in the elderly.

The human brain normally produces the amyloid- peptide as part of neuronal function, but these peptides are routinely cleared from the brain, in large part, through the blood vessels. However, in most Alzheimer's patients, the brain's ability to clear amyloid-β is impaired and, consequently, one type of amyloid-β (Aβ42) accumulates in amyloid plaques and another type (Aβ40) collects in brain arteries, resulting in CAA.

The research team found that CD36, a protein located on the surface of immune cells and in blood vessels, is key to the buildup of Aβ40 in blood vessels. The protein is part of the innate immune system; its function is to act as a sensor to detect molecules that represent a danger to the host. Some of these molecules are derived from invading organisms, such as infectious agents, but some are produced by the body, such as amyloid peptides that, in excess amounts, could become toxic.

"CD36 is a scavenger protein that binds threatening molecules and activates a host of cellular responses designed to get rid of the threat," Dr. Iadecola says. "Such responses include ramping up inflammation and

producing free radicals, both aimed at neutralizing the offenders. However, in the case of amyloid-β, inflammation and free radicals damage brain blood vessels and prevent the efficient clearance of the peptide through these vessels. This, in turn, sets up a vicious circle that favors the vascular accumulation of the amyloid-β peptide and promotes CAA."

Dr. Iadecola and his colleagues say it may be possible to design new drugs that bind to CD36 on the precise site on the protein's structure that amyloid-β sticks to, thus blocking the deleterious effects of receptor activation. "We now know how it occurs, and so now we have a new target," he says.

Provided by Weill Cornell Medical College