

Health & Physiology

Unexpectedly stalled: the dynamics of brain blood flow in Alzheimer's disease

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ABSTRACT

A reduction in brain blood flow is a long-known symptom of Alzheimer's disease that has remained unexplained. Using mouse models of Alzheimer's, we discovered the cellular mechanism that causes this brain blood flow reduction and further showed that increasing brain blood flow improves memory function.



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Alzheimer's disease is characterized by a progressive loss of memory and cognitive function, and although much is known about the underlying mechanisms that contribute to this brain dysfunction, no effective therapies exist. It has been known for decades that blood flow to the brain is reduced by about one-third in patients with Alzheimer's disease. This is a large reduction in blood flow, similar in size to the brain blood flow decrease that causes the transient dizziness sometimes experienced when standing up too quickly after lying down. This blood flow deficit likely contributes to the cognitive symptoms of

Alzheimer's, although the cause has remained poorly understood.

To study the cause and consequence of blood flow reductions in Alzheimer's, we used genetically engineered mice that develop many symptoms of the disease, including the formation of [amyloid plaque deposits](#) (one pathological hallmark of Alzheimer's), brain blood flow reductions, and memory impairment. We measured brain blood flow in these mice while they were alive by surgically removing a part of the skull, placing a glass window on top of the brain, and imaging the brain

vasculature and the motion of blood cells in those blood vessels. This imaging used advanced optical microscopy techniques that enabled us to see every vessel in a small volume of the mouse brain, from arteries and veins down to individual capillaries where blood cells flow single file.

We looked for blockages in different classes of blood vessels to determine where this reduction in brain blood flow in the Alzheimer's mice originated. We found that the smallest blood vessels – capillaries – were the ones that were sometimes occluded, with about 2% of capillaries stalled, which was five times the number of non-flowing capillaries in normal, control mice. Although only a couple percent of capillaries had stalled blood flow in the Alzheimer's mice, each stalled vessel led to decreased blood flow in multiple downstream vessels, magnifying the impact on overall brain blood flow. To understand what cell-type caused stalled capillaries, we fluorescently labeled different blood cells and identified one class of white blood cells (neutrophils) to be the most common cell type causing occluded blood vessels. We then serendipitously identified an antibody that blocks the adhesion of these white blood cells. With a single injection of these antibodies the stalled capillaries started flowing again and brain blood flow speeds quickly increased by about 20%. These findings suggest that the brain blood flow decreases in Alzheimer's may be due to white blood cells sticking in brain capillaries.

To determine the impact of these capillary stalls on cognitive function, we asked if the restoration of brain blood flow has an impact on the performance

of Alzheimer's disease mice on memory tasks. We found that memory function in tests for short-term memory was improved – up to the level of the non-Alzheimer's disease control mice – within hours of giving the antibody that eliminated the capillary stalls and improved brain blood flow. This rapid improvement in memory function after increasing brain blood flow was seen even in aged mice with more advanced stages of Alzheimer's pathology.

While these findings highlight the critical importance of treating vascular dysfunction in neurodegenerative diseases, much work is needed before we can say what relevance our findings may have for Alzheimer's patients. First, while the vascular inflammation that likely leads to the capillary stalls has been seen in both patients with Alzheimer's and in mouse models of the disease, we do not yet know if capillary stalls occur or contribute significantly to the brain blood flow reductions seen in Alzheimer's patients. We also do not know if increasing brain blood flow would lead to as big of an improvement in memory function in patients as we saw in the Alzheimer's mice. Our insight that white blood cell adhesion is a cause of the decreased brain blood flow in Alzheimer's mice will, however, guide screens for potential therapies that could be tried in humans.

These findings point to the important role brain blood flow disruptions play in dementia and open the door to new therapeutic opportunities for Alzheimer's disease patients.