Blocking protein curbs memory loss in old mice

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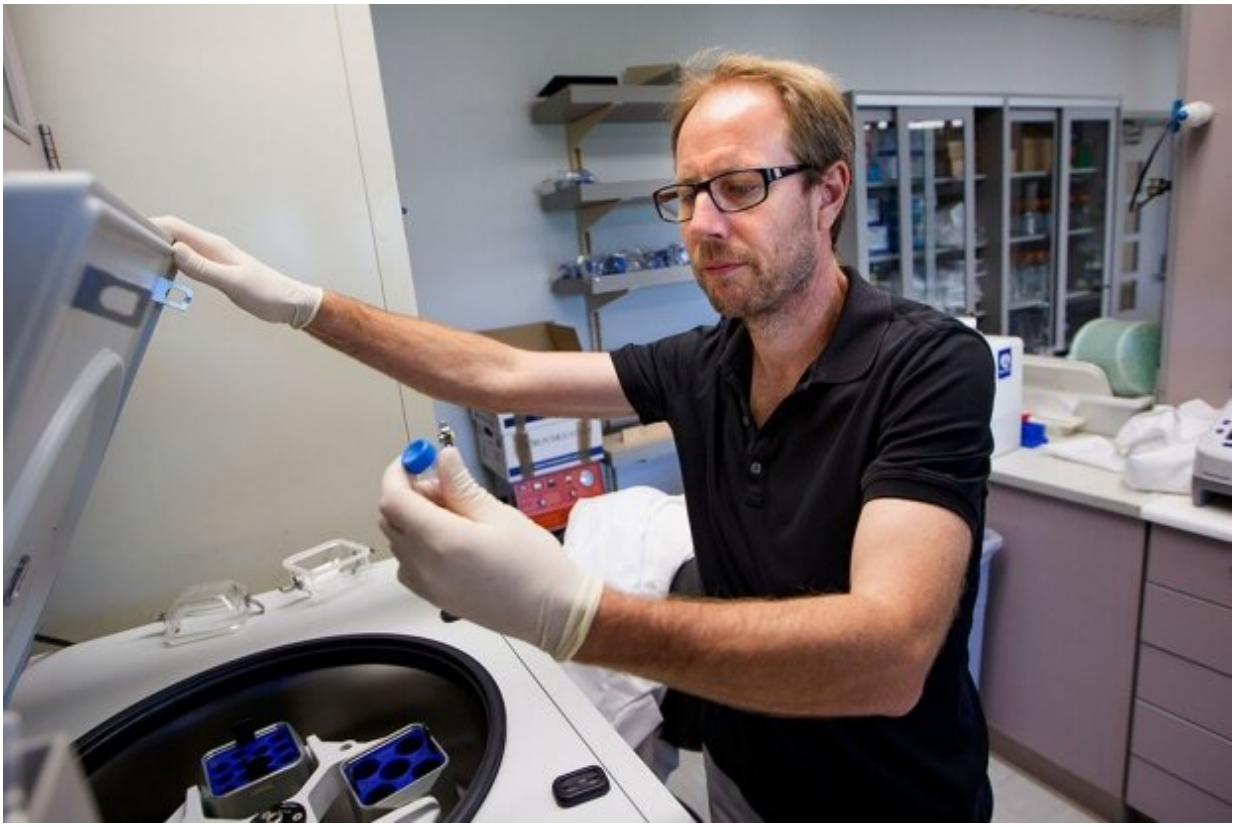

New research from Tony Wyss-Coray and his collaborators shows that older mice performed better on memory tests when a protein found on the walls of blood vessels in the brain was blocked. Credit: Norbert von der Groeben

Impeding VCAM1, a protein that tethers circulating immune cells to

blood vessel walls, enabled old mice to perform as well on memory and learning tests as young mice, a Stanford study found.

Mice aren't people, but like us they become forgetful in old age. In a study published online May 13 in *Nature Medicine*, old mice suffered far fewer senior moments during a battery of memory tests when Stanford University School of Medicine investigators disabled a single molecule dotting the mice's cerebral blood vessels. For example, they breezed through a maze with an ease characteristic of young adult mice.

The molecule appears on the surfaces of a small percentage of endothelial cells, the main building blocks of blood vessels throughout the body. Blocking this molecule's capacity to do its main job—it selectively latches onto immune cells circulating in the bloodstream—not only improved old mice's cognitive performance but countered two physiological hallmarks of the aging brain: It restored to a more youthful level the ability of the old mice's brains to create new nerve cells, and it subdued the inflammatory mood of the brain's resident immune cells, called microglia.

Scientists have shown that old mice's blood is bad for young mice's brains. There's a strong suspicion in the scientific community that something in older people's blood similarly induces declines in brain physiology and cognitive skills. Just what that something is remains to be revealed. But, the new study suggests, there might be a practical way to block its path where the rubber meets the road: at the blood-brain barrier, which tightly regulates the passage of most cells and substances through the walls of blood vessels that pervade the human brain.

"We may have found an important mechanism through which the blood communicates deleterious signals to the brain," said the study's senior author, Tony Wyss-Coray, Ph.D., professor of neurology and neurological sciences, co-director of the Stanford Alzheimer's Disease

Research Center and a senior research career scientist at the Veterans Affairs Palo Alto Health Care System. The lead author of the study is Hanadie Yousef, Ph.D., a former postdoctoral scholar in the Wyss-Coray lab.

The intervention's success points to possible treatments that could someday slow, stop or perhaps even reverse that decline. Targeting a protein on blood-vessel walls may be easier than trying to get into the brain itself.

"We can now try to treat brain degeneration using drugs that typically aren't very good at getting through the blood-brain barrier—but, in this case, would no longer need to," Yousef said.

Different way of reaching the brain

The researchers focused on the mouse hippocampus, a well-studied brain structure that's essential to memory and learning and whose architecture and function are similar in mice and humans. The hippocampus is also one of the very few sites in the adult mammalian brain where neurogenesis, the creation of new nerve cells, occurs; those new cells are critical to the formation of new memories.

Since his lab first began reporting several years ago that unknown factors in old blood can accelerate cognitive decline and, conversely, that factors in young blood can rejuvenate old brains, Wyss-Coray, the D.H. Chen Professor II, has sought to identify those factors. But he and his colleagues took a different tack in the new study.

He said the roughly 400 miles of blood vessels that pass through the human brain differ from those elsewhere in the body in one important respect: They're much more selective about what gets in and what comes out.

"The blood-brain barrier excludes most bloodborne cells and substances," he said. "We wondered if, instead of entering the brain and monkeying with brain cells directly, something in circulating blood could be communicating directly with the brain's endothelial cells."

A few years ago, Wyss-Coray and his colleagues compared blood from young and old people to pinpoint substances whose abundance changes with age. In the new study, they narrowed their search to just those age-associated bloodborne substances that are in some way directly related to vascular function. Topping the list was a circulating form of a protein constantly produced within endothelial cells and displayed on their surfaces.

The protein, VCAM1, is well known to immunologists. It's a docking station for circulating cells of the immune system—a first stop in a passport-punching process that under certain relatively rare conditions grants those immune cells permission to migrate across the brain's otherwise tightly closed border.

This protein gets sawed off of endothelial cell surfaces and dumped into the bloodstream by lawnmowerlike enzymes at pretty much the same rate it gets produced, so its population size on blood vessels remains relatively constant. But VCAM1's abundance on blood vessel surfaces jumps markedly in the event of local injury or infection. That snags immune cells, which combat infectious pathogens and are essential to the healing process.

"At any given time, levels of circulating VCAM1 are a good proxy for the total amount of VCAM1 on the body's blood-vessel endothelial cell surfaces," Wyss-Coray said. Previous studies have linked high circulating VCAM1 levels to cancer, heart disease, stroke, Alzheimer's disease, epilepsy and other inflammatory disorders.

Identifying the source of dysfunction

In the study, the researchers showed that VCAM1's abundance on the endothelial cells comprising blood vessel walls in the mouse brains rises in old age, as well as in the brains of younger mice that are given infusions of older mice's plasma, the cell-free, liquid portion of blood. Likewise, the researchers observed increased signs of inflammation in the older mice's cells.

Wyss-Coray suspects that the tethering of immune cells to blood-vessel surfaces—particularly if immune cells are in an activated state due to an existing condition, such as injury or infection, or to old age—enhances the release of inflammatory proteins that penetrate blood vessel walls via specialized receptors on endothelial-cell surfaces.

Circulating VCAM1, though, wasn't the source of brain dysfunction. When the investigators depleted old mice's plasma of the protein before giving the plasma to young mice, they observed the same damaging effects in the hippocampus—reduced neurogenesis, increased microglial inflammation—they'd previously seen when young mice received old plasma.

Deleting the gene encoding VCAM1 in mice brains prevented the protein's production in the brain's endothelial cells. If this deletion was performed in young adulthood, the mice no longer suffered reduced neurogenesis or increased microglial inflammation when they grew older.

The researchers achieved the same results with monoclonal antibodies, specialized proteins that bind avidly and exclusively to their target. Three weeks of treatment with a monoclonal antibody directly targeting and blocking VCAM1 was enough to increase neurogenesis and diminish microglial reactivity in older mice's hippocampi.

These mice aced a battery of mental-acuity tests. One test, the Barnes maze, involves a table from which mice want to escape. The table has lots of holes through which the mouse can fall a short distance onto the floor (although not far enough to cause an injury). But one hole connects to a tube mounted horizontally under it, providing a comforting escape to the mice. The mouse must learn and remember how to get to the "safety" hole.

Once they were fully trained, older mice treated with this antibody reached the escape hole in the Barnes maze as quickly as young mice.

"Blocking VCAM1 in the brain wound up making these mice smarter," Wyss-Coray said. "In all the time I've been working on this, I've never seen such performance before."

More information: Hanadie Yousef et al. Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1, *Nature Medicine* (2019). DOI: 10.1038/s41591-019-0440-4

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