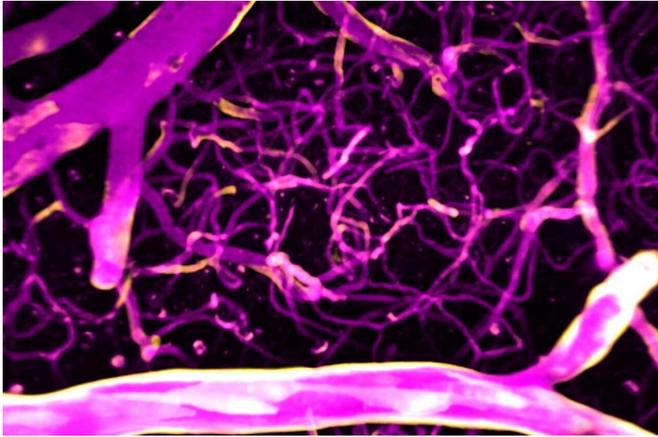


Study finds calcium precisely directs blood flow in the brain

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Calcium (pink) directs blood flow in the brain's blood vessels. Credit: Thomas Longden

Unlike the rest of the body, there is not enough real estate in the brain for stored energy. Instead, the brain relies on the hundreds of miles of blood vessels within it to supply fresh energy via the blood. Yet, how the brain expresses a need for more energy during increased activity and then directs its blood supply to specific hot spots was, until now, poorly understood.

Now, University of Maryland School of Medicine and University of Vermont researchers have shown how the [brain](#) communicates to [blood vessels](#) when in need of energy, and how these blood vessels respond by relaxing or constricting to direct blood flow to specific brain regions.

In their new paper, published on July 21 in *Science Advances*, the researchers say that understanding how the brain directs energy to itself in intricate detail can help determine what goes wrong in conditions like Alzheimer's disease and dementia, where faulty blood flow is a predictor for cognitive impairment. If the brain does not get blood to where it needs it when it needs it, the neurons

become stressed, and over time they deteriorate ultimately leading to cognitive decline and memory problems.

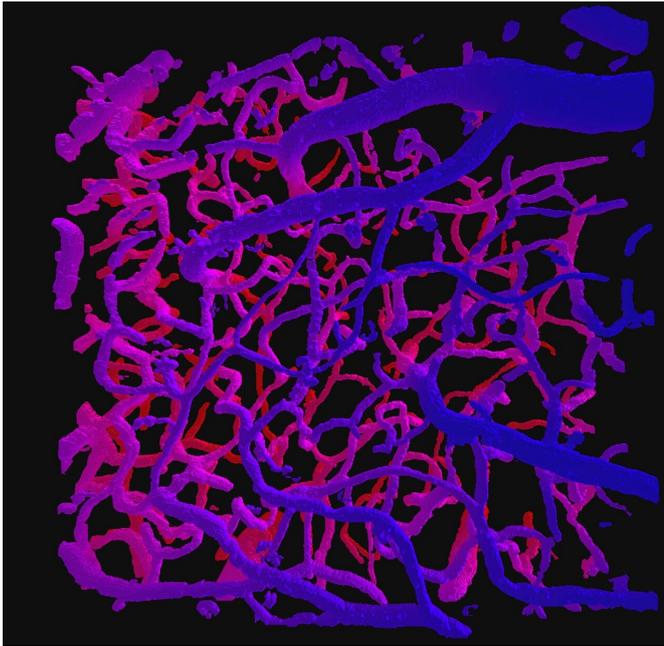
Large arteries feed medium-sized vessels known as arterioles that then feed even tinier capillaries—so small that only a single blood cell can pass through at once. In a 2017 *Nature Neuroscience* paper, the researchers showed that electrical pulses coursing through the capillaries direct blood flow from the medium-sized arterioles supplying large regions of the brain. For this latest paper, the team wanted to study the fine-tuning of blood as it flows through the capillaries to precisely regulate energy supply to tiny regions in the brain.

"There seem to be two mechanisms working in tandem to ensure that energy in the form of blood makes it to specific regions of the brain: one broad and the other precise," says Thomas Longden, Ph.D., Assistant Professor of Physiology at University of Maryland School of Medicine. "The first electrical mechanism is like a crude sledgehammer approach to get more blood to the general vicinity of the increased brain activity by controlling the medium-sized arterioles, and then capillary calcium signals ensure exquisite fine-tuning to make sure the blood gets to exactly the right place at the right time through the tiny capillaries."

Dr. Longden and his collaborators used a protein which emits green light when calcium increases in the cell. Due to the efforts of Michael Kotlikoff's team at Cornell University, they were able to turn this tool on in the cells lining blood vessels of mice. The researchers then looked through little windows in the brains of these mice to investigate calcium's role in controlling blood flow in the brain's capillaries. When the cells lining the blood vessels received an influx of calcium, they glowed green. They detected 5,000 calcium signals per second in the capillaries in the tiny section of brain visible through the window, which they say amounts to

about 1,000,000 of these responses each second in the entire brain's blood [vessel](#) system.

"Until we deployed this new technology, there was this wholly unseen world of calcium signaling in the brain hidden from view, and now we can see a ton of activity within the brains blood vessels—they are constantly firing," says Dr. Longden.



Blood vessels in the brain. Credit: Thomas Longden

Dr. Longden and the research team then dissected the intricate cellular mechanism behind calcium's role in directing blood branch-by-branch through the tiny vessels of the brain. They found that when neurons fire electrical signals, they cause an increase in calcium in the cells lining the blood vessels. Then enzymes detect this calcium and direct the cells to make nitric oxide. Nitric oxide is a hormone (and a gas) that causes muscle-like cells around blood vessels to relax, which then widens the vessels allowing more blood to flow in.

"Capillaries were traditionally thought as simple conduits for red blood cells, and the barrier between the blood and brain," says co-senior author Mark T. Nelson, Ph.D., University of

Vermont Distinguished Professor and Chair of Pharmacology. "Here, we revealed an unknown universe of calcium signaling in capillaries, and much like traffic lights, these [calcium](#) signals direct vital nutrients to nearby active neurons."

"The first step towards figuring out what goes wrong in diseases is to determine how the system works as it normally should," says E. Albert Reece, MD, Ph.D., MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "Now that the researchers have a handle on how this process works, they can begin to investigate how the [blood](#) flow is disrupted in Alzheimer's disease and dementia in order to figure out ways to fix it."

More information: "Local IP3 receptor-mediated Ca²⁺ signals compound to direct blood flow in brain capillaries" *Science Advances* (2021). advances.sciencemag.org/lookup.../1126/sciadv.abh0101

Provided by University of Maryland School of Medicine

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