Bottleneck in blood supply makes brain vulnerable to strokes

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A team of University of California, San Diego physicists and neuroscientists has discovered a bottleneck in the network of blood vessels in the brain that makes it vulnerable to strokes. The finding may explain the origin of the puzzling damage to the brain's gray matter often detected in brain scans, especially among the elderly.

In the study, published this week in the journal *Proceedings of the National Academy of Sciences*, the researchers used a laser technique they developed to precisely monitor changes in blood flow resulting from an induced blockage in a tiny artery, or arteriole, in the brains of anesthetized rats. They found that the penetrating arterioles, which connect the blood vessels on the brain's surface with deeper blood vessels, are a vulnerable link in the network.

"The blood vessels on the surface of the brain are like a collection of city streets that provide multiple paths to get somewhere," explained David Kleinfeld, a professor of physics at UCSD, who led the team. "If one of the vessels is blocked, blood flow quickly rearranges itself. On the other hand, the penetrating arterioles are more like freeways. When blocked, the blood flow is stopped or slowed significantly in a large region round the clot."

The obstruction of blood flow resulted in damage to the surrounding brain area, which the researchers report resembled damage seen in the brains of humans and thought to be the result of "silent strokes." Silent strokes have attracted attention recently because magnetic resonance imaging has made it possible to follow changes in the brains of individuals as they age. MRI scans have revealed that, over time, small holes accumulate in the gray matter of many patients, including those who have no obvious behavioral signs of a stroke.

The researchers say their results support the hypothesis, made by clinicians, that the penetrating arterioles may be the location of small strokes that cause the death of sections of brain tissue in humans. The accumulation of damage may lead to memory loss, and may be a risk factor for having a larger stroke, according to Pat Lyden, a professor of neurosciences at UCSD's School of Medicine and head of the UCSD Stroke Center.

"This damage is an enormous problem," said Lyden, who collaborated with Kleinfeld on the study. "We think it is part of the dementia picture in Alzheimer's and non-Alzheimer's patients. But until now, we had no insight into the mechanism of the damage, and understanding the mechanism is the first step toward understanding how to prevent it."

To determine what happens in the brain during a stroke, the researchers created a tiny clot in a blood vessel in the brain of an anesthetized rat. They used focused laser light to excite a dye they had injected into the bloodstream. A chemical reaction of the excited dye "nicked" the blood vessel at the target location and triggered the natural clotting response.

"The technique creates a clot while generating very little collateral damage," said Beth Friedman, an associate project scientist working with Lyden in neurosciences and a contributing author on the paper. "Then we can study blood flow changes to understand what is happening in the brain in real time."

Before and after the formation of the clot, the researchers tracked the movements of red blood cells using two-photon fluorescence microscopy. Two-photon fluorescence microscopy is a powerful imaging tool that uses brief (less than one-trillionth of a second) laser pulses to peer below the surface of the brain.

In contrast to a previous study, in which the team showed there was very little disruption in blood flow when a clot formed in the blood vessels on the surface of the brain, a blockage in the penetrating arterioles had a significant effect. The flow of red blood cells was reduced far downstream of the blockage. Because blood flow cannot simply take alternate routes to compensate for the blockage, the penetrating arterioles are a bottleneck in the blood supply to gray matter.

"In this study, we took advantage of being able to see into individual capillaries in brain tissue," explained Nozomi Nishimura, who was a graduate student working with Kleinfeld in physics at the time of the study. "It is the capillaries, the smallest blood vessels, that provide the brain cells with oxygen and nutrients. So we were able to measure the dynamics of blood flow where it really matters to nerve cells."

Source: University of California - San Diego