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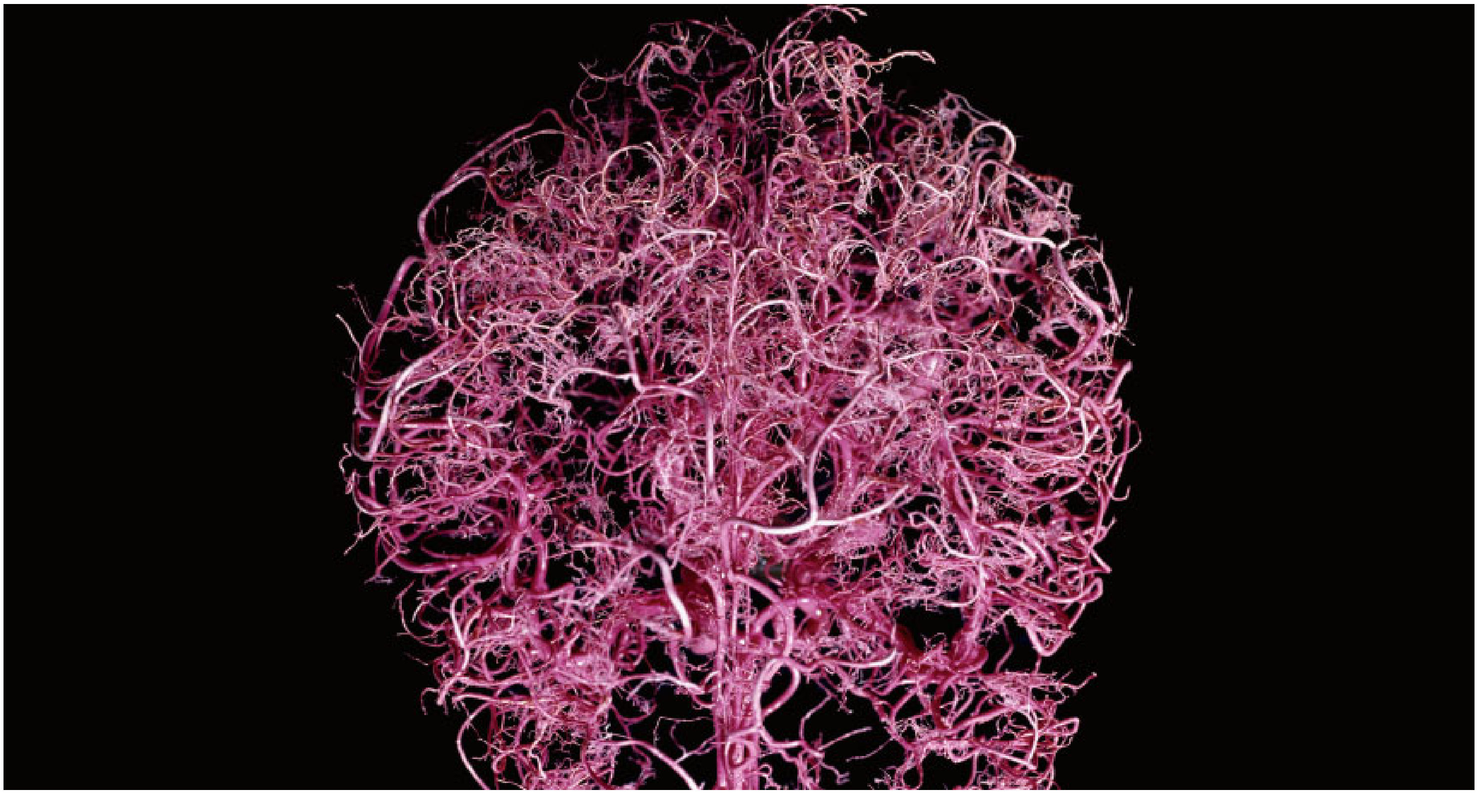
Feature: Neuroscience,Health

Blood exerts a powerful influence on the brain

The brain's nerve cells have a call-and-response relationship with the blood that sustains them

By Laura Sanders 11:15am, November 4, 2015



HEAD RUSH Blood vessels run through the brain delivering oxygen and nutrients — and maybe even commands — to nerve cells.

Magazine issue: Vol. 188 No. 10, November 14, 2015, p. 22

Blood tells a story about the body it inhabits. As it pumps through vessels, delivering nutrients and oxygen, the ruby red liquid picks up information. Hormones carried by blood can hint at how hungry a person is, or how scared, or how sleepy. Other messages in the blood can warn of heart disease or announce a pregnancy. Immune molecules can reveal an infection.

When it comes to the brain, blood also seems to be more than a traveling storyteller. In some cases, the blood may be writing the script.

A well-fed brain is crucial to survival. Blood ebbs and flows within the brain, moving into active areas in response to the brain's demands for fuel. Now scientists have found clues that blood may have an even more direct and powerful influence. Early experiments suggest that, instead of being at the beck and call of nerve cells, blood can actually control them. This role reversal hints at an underappreciated layer of complexity — a layer that may turn out to be vital to how the brain works.

The give-and-take between brain and blood appears to change with age and with illness, researchers are finding. Just as babies aren't born walking, their developing brain cells have to learn how to call for blood. And a range of age-related disorders, including Alzheimer's disease, have been linked to dropped calls between blood and brain, a silence that may leave patches of brain unable to do their jobs.

This line of research is expanding scientists' view of what makes the brain tick, and the implications for human health are enormous. Diabetes, multiple sclerosis and hypertension— diseases that harm blood vessels elsewhere in the body — may afflict the brain too. What's more, common drugs that tinker with blood flow, including statins, anti-inflammatories and even Viagra, may affect how the brain operates.

In Vancouver this summer, neuroscientist and biomedical engineer Elizabeth Hillman of Columbia University attended a meeting devoted to blood flow in the brain. Though the field is full of unanswered questions, "there was a palpable sense we were getting somewhere," Hillman says.

Flow control

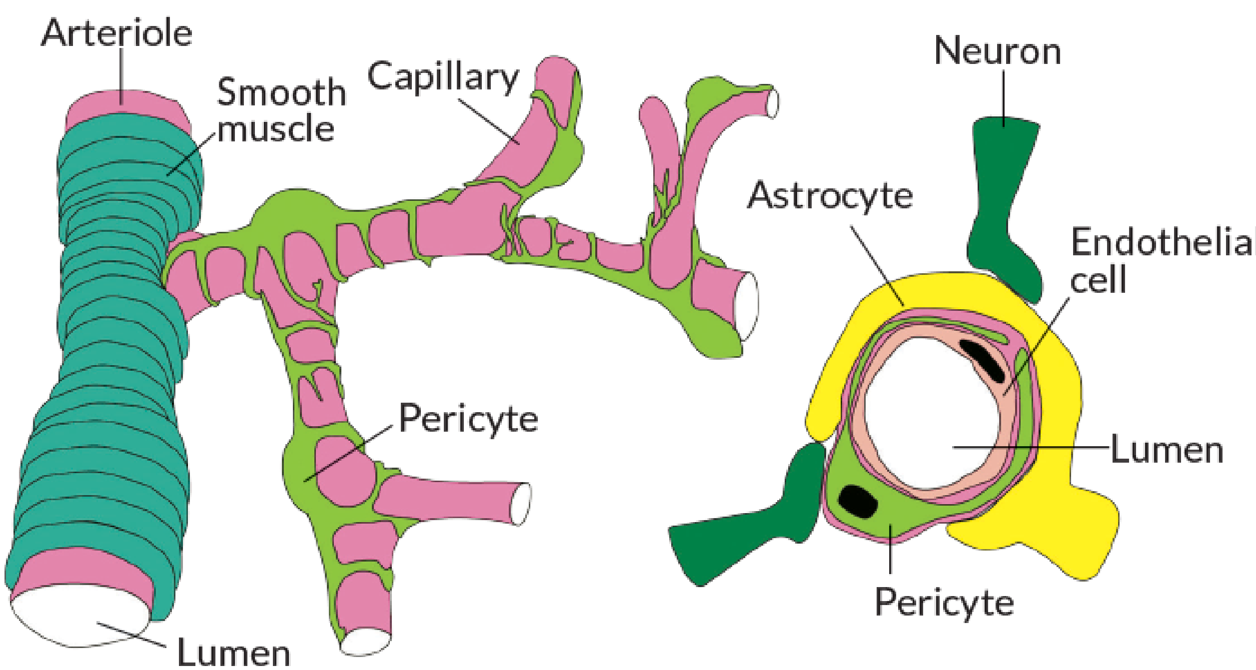
When nerve cells, or neurons, are active, they call for more blood by somehow signaling to nearby vessels. The vessels respond by widening and allowing more blood to flow. This blood beckoning forms the basis of a brain-scanning technique called functional MRI, which measures blood flow as a proxy for neural activity.

When delivering fuel such as glucose and oxygen to hungry neurons, blood first pumps into large arteries that run along the outside of the brain. It then plunges inward through smaller vessels called arterioles before squeezing down into capillaries so thin that red blood cells must travel single file.

Story continues below graphic

The squeeze

The cells in and around the brain's blood vessels somehow carry messages that change blood flow. Scientists scrutinizing the role of astrocytes, smooth muscle cells, pericytes and endothelial cells, which surround the lum the channel where blood flows.

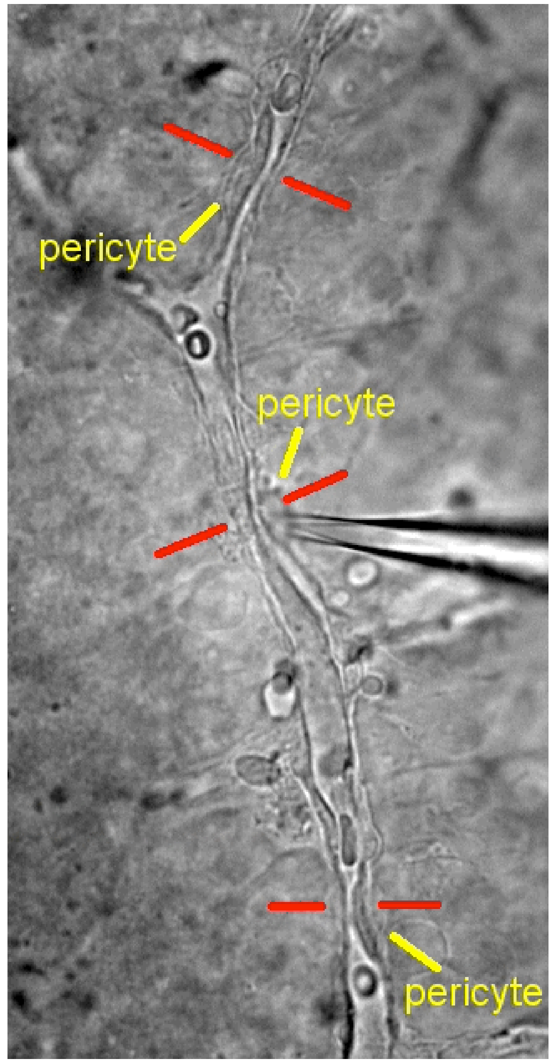


N.B. Hamilton, D. Attwell, C.N. Hall/Front. Neuroenergetics 2010

Textbooks about the brain often point to star-shaped cells called astrocytes as the middlemen that carry the message — "more blood, please" — from neurons to arterioles. Astrocytes (*SN: 8/22/15, p. 18*) are often found tangled up with both neurons and blood vessels, a perfect spot for a go-between.

But the idea that astrocytes complete the connection between neurons and larger blood vessels may be too simple. Much still remains mysterious about this neuron-to-blood messaging. There's no consensus yet on how neurons come up with the request, which molecules carry the signal or which cells respond to it, though scientists are turning up plenty of suspects.

Neuroscientist David Attwell of University College London and colleagues have started focusing on cells called pericytes, which dot the outside of capillaries throughout the body. Pericytes, best known in the brain for their role in forming the blood-brain barrier, also have a hand in delivering blood by controlling capillaries, Attwell and colleagues proposed last year in *Nature*. Capillaries were larger and let more blood flow in places where pericytes resided, suggesting that the cells could control the floodgates, the team found.



AND SQUEEZE After stimulation, specialized cells called pericytes constrict vessels and curb blood flow, some studies have found.

C. Peppiatt et al/Nature 2006

That idea is controversial. Neuroscientists Robert Hill and Jaime Grutzendler of Yale University and colleagues published a paper in July in *Neuron* claiming that pericytes cannot dish out blood. Pericytes lack actin, a contractile protein that would be needed to squeeze or relax vessels, the researchers argue. Smooth muscle cells that line vessels larger than capillaries control blood flow, they say.

Then there are the endothelial cells, which may also help regulate blood flow. Unlike astrocytes and pericytes, which live outside of vessels, endothelial cells are stitched into the very fabric of blood vessels large and small. As the innermost layer of all the blood vessels in the body, endothelial cells are perfectly poised to detect chemical signals from their surroundings and carry ultrafast messages along vessels, Hillman says.

When Hillman and her colleagues damaged the endothelial cells lining an artery on the surface of a rat's brain, blood no longer responded to busy neurons. Vast networks of endothelial cells may carry messages lightning-quick from neurons that need fuel to distant large arteries that can supply it. Those results, published in 2014 in the *Journal of the American Heart Association*, suggest that the same system that regulates blood flow in the rest of the body might also apply to the brain. "The real irony is that [people thought] there was somehow this divide" between body and brain, Hillman says.

Newborn brains can't do it

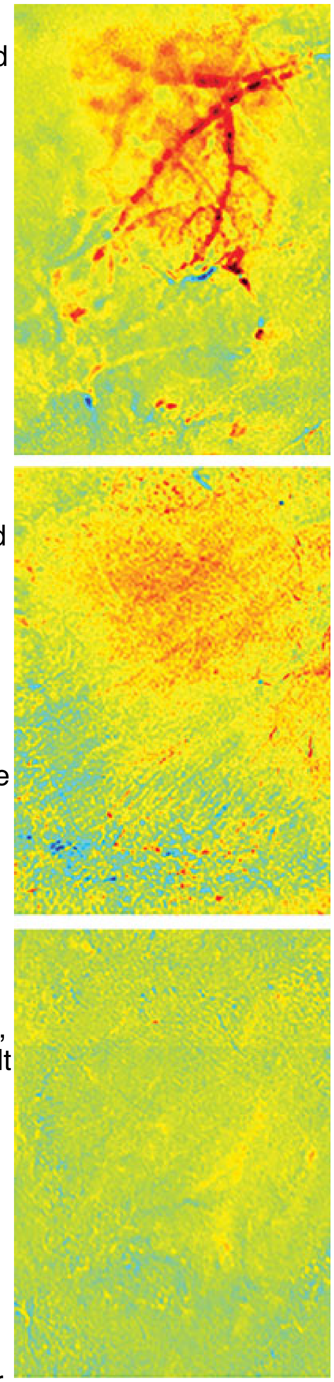
As Attwell and others try to work out how neurons call for blood, other research is showing that this skill is not part of a newborn's repertoire — and maybe for good reason. In the days and weeks after birth, the communication wires between blood vessels and neurons are put down with precise specifications, recent studies suggest. The fact that this system takes time to grow helps explain why young babies' brains give off funny results during an fMRI scan. Instead of sparking an influx of blood, neural activity in a baby's brain can cause what looks like blood leaving the area.

"There's a whole bunch of odd goings-on in the very young brain," Hillman says. These puzzling negative signals hint that the infant brain has its own surprising way of operating.

In very young rats, active neurons can't call blood for nutrients, Hillman and colleagues reported in the *Proceedings of the National Academy of Sciences* in 2013. "If the neurons are trying desperately to fire in response to the stimulus, but they simply don't get the energy they need to do it, they have to stop. That's what it looks like to us," she says. "It looks like they give up."

A pause may be its own kind of signaling, perhaps laying the groundwork for a fully functioning adult brain. As the rats grew up, their neurons' hunger cries were answered. Blood flooded the area soon after neurons fired, the team found.

This interaction between neuron and blood can lead to more blood delivered not just by turning up the flow, but also by creating new pipes, a different study reveals. Neurons that respond to whisker twitches in young mice could actually trigger new blood vessels to form, neuroscientist Chenghua Gu of Harvard University and colleagues found. When the researchers plucked a whisker so that its corresponding neurons were deprived of input, neurons sensitive to that whisker remained silent. Those inert neurons had fewer nearby blood vessels than neurons that were handling incoming information normally, Gu and colleagues reported in 2014 in *Neuron*. But if the scientists flicked a whisker, sparking lots of activity in the associated neurons, blood vessels sprouted new branches and delivered blood to the active cells. In the growing brain, neurons are literally drawing blood to themselves, the results suggest. "You're building more roads," Gu says.



FEED ME Blood rich in hemoglobin (red) rushes into a patch of brain in an adult rat after its paw is stimulated (top panel). In adolescents, the signal is just beginning to emerge (middle). In newborn rats, when neurons call for blood, the request goes unanswered (bottom panel). *M. Kozberg et al/PNAS 2013*

The results make sense to Hillman. "If you were building a city, you wouldn't put in all the sewers and all the electronics before the houses are built," she says. "You let the houses get built, and then you provide each house with what it needs."

It's not clear exactly how the young neurons will vessels into existence, but Gu has an idea. She thinks that the low-oxygen state that results from the neurons cranking away without fuel might be the key signal. While it might sound alarming to think of patches of starving neurons within babies' brains, that desperate state might be the impetus for blood vessel growth. If so, the recent findings might ultimately point to optimal dosages of oxygen for young babies born in distress. Too much might interfere with blood vessel formation, Hillman says.

Blood takes the wheel

Beyond keeping neurons well fed, blood may actually tell neurons when to fire. Kind of like gasoline oozing out of a car's gas tank and taking the wheel.

The idea isn't as crazy as it sounds, says neuroscientist Christopher Moore of Brown University. In 2008, he and colleague Rosa Cao laid out their "hemo-neural hypothesis" in the *Journal of Neurophysiology*. The gist is that blood may influence the behavior of neurons in a way that goes beyond just providing energy to already active cells.

"The blood has exquisite access to where we stand," Moore says. Replete with hormones, sugar and other signals, the blood contains an accurate readout of what the body needs. It makes sense that this complex system would be able to influence its neural neighbors. "It would be amazingly stunning if there was a neuron-to-vascular effect and no vascular-to-neuron effect," he says.

In the last few years, he and his group have caught glimpses of that reversed effect. In Moore's lab, neuroscientist Tyler Brown led projects to change blood flow by tweaking the size of vessels. A slight dilation or constriction of vessels reliably changes the behavior of nearby neurons. The team used optogenetics (*SN: 1/30/10, p. 18*) to squeeze blood vessels by activating endothelial or smooth muscle cells that were genetically modified to respond to light. Tweaking the vessels caused some nearby neurons to dial their behavior up or down, the team reported last year in Washington, D.C., at the annual meeting of the Society for Neuroscience.

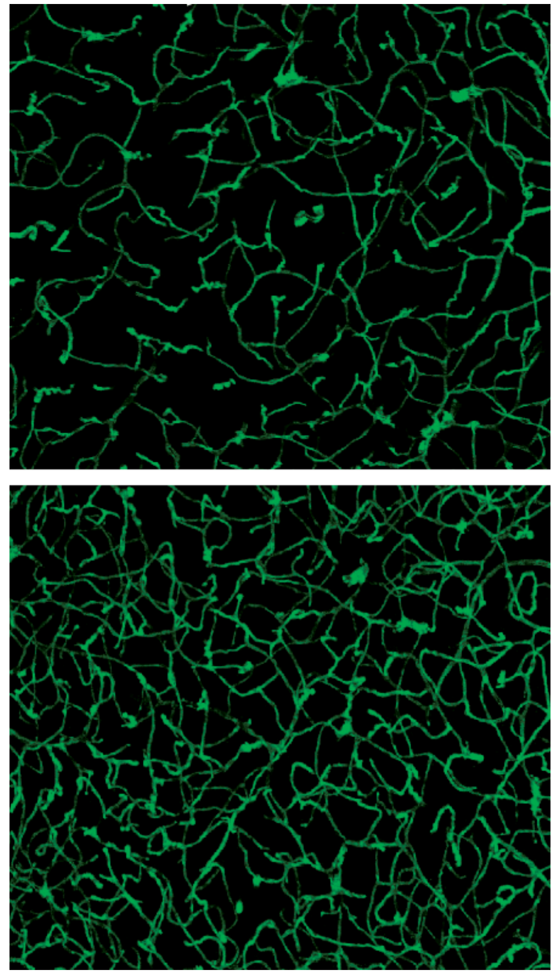
Figuring out the details of these blood-to-neuron commands will take a long time, Moore says. "We still don't know how a neuron being active draws a blood vessel, and people have been working on that forever."

Talking about blood directing the brain is odd in the context of the normal working brain, says Hillman. "Does the blood somehow make decisions for the brain?" she asks. But for catastrophic events like strokes, the concept is obviously true. "When you think about it in terms of diseases and disorders, it makes a lot of sense."

Scientists are starting to investigate blood flow troubles in dementia, suspicious that cognitive problems may stem from lost conversations between neurons and blood. Abnormal blood flow in the brain is present in the five major forms of dementia, including Alzheimer's disease and dementia with Lewy bodies. This idea isn't new: In the early

1900s, Alois Alzheimer suggested that problems in the circulatory system might trigger the memory-robbing disease now named for him.

Story continues below graphic

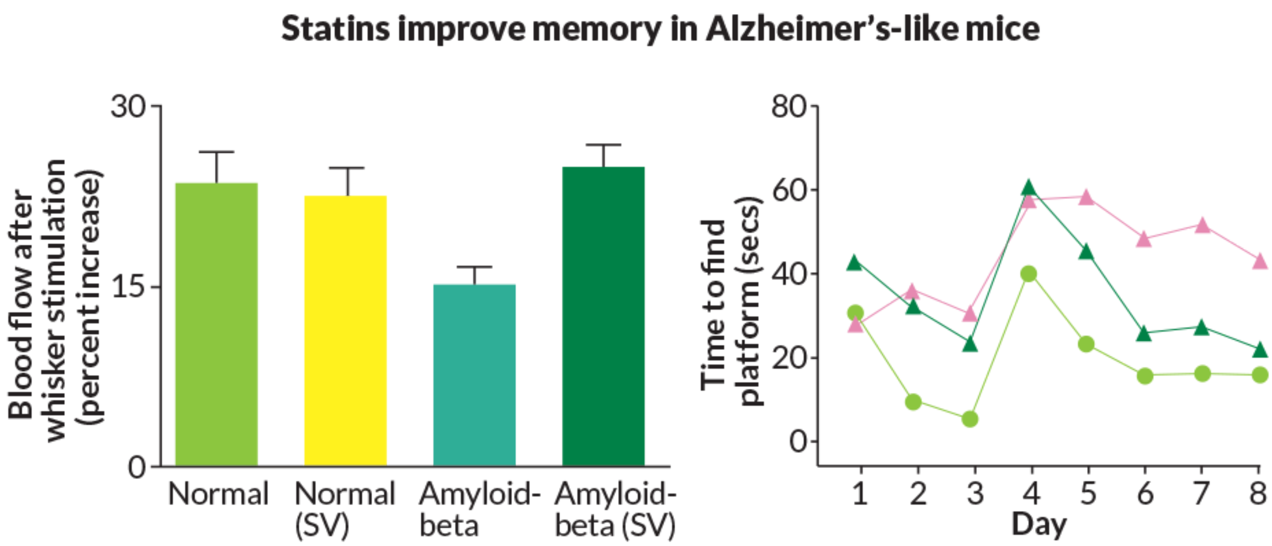


STIMULATING GROWTH Blood vessel networks branched less and were shorter in the brains of mice that had no sensory stimulation (top). In the brains of mice that got many whisker flicks (bottom), vessels were more plentiful.

B. Lacoste/Harvard Medical School

Protecting memory

Among adult mice engineered to show signs of Alzheimer's (teal and dark green bars, left), blood flow responc more readily to neural signals in those receiving a statin drug (SV) than those receiving no drug. The statin-tre mice (dark green line, right) also found a previously visited hidden platform faster than mice receiving no statin (pink). Light green shows normal mice with no signs of Alzheimer's.



Source: Xin-Kang Tong *et al/J. Neurosci.* 2012

Other disorders, such as diabetes, might harm the brain by damaging blood vessels. Many scientists attribute the mental fuzziness that can accompany diabetes to neuron damage from excess glucose. But maybe faulty lines between unresponsive blood vessels and neurons are to blame, Hillman says.

Common drugs that influence blood flow may also have unanticipated effects on the brain. In addition to statins, drugs such as Viagra, blood pressure drugs and even anti-inflammatories may unintentionally change how the brain operates. These drugs may be dampening the brain's ability to call for blood when it needs it, Hillman says. "That could have a long-term effect that I don't think anybody is thinking about right now."

There's also the possibility that some blood-modulating drugs may have beneficial brain effects. Blood vessel–clearing statins, for instance, may help protect memory in people with Alzheimer's disease.

Statin treatment improved the memory of middle-aged mice engineered so their brains produce gobs of sticky amyloid-beta, the protein that piles up in people with Alzheimer's. Three months on the statin simvastatin restored short- and long-term memory in these mice, neuroscientist Edith Hamel of McGill University in Montreal and colleagues reported in 2012.

Compared with mice that didn't get the treatment, the mice on statins also had healthier blood vessels in their brains that seemed more responsive to changes in neuron activity. Though the idea remains controversial, a similar effect may happen in people. Several studies have linked statins taken in early old age to lower rates of Alzheimer's later on.

Because it's so easy to get drugs into the bloodstream, the promise of changing the brain by changing the blood is great. And these early hints of how blood vessels and neurons work together are bringing scientists closer to that alluring goal. Though there is still much to learn, one thing is already clear: Together, the blood and brain are telling a compelling story.

This article appears in the Nov. 14, 2015, Science News *with the headline, "Head rush: Blood exerts a powerful influence on the brain."*

Citations

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