Unexpected discovery opens a new way to regulate blood pressure

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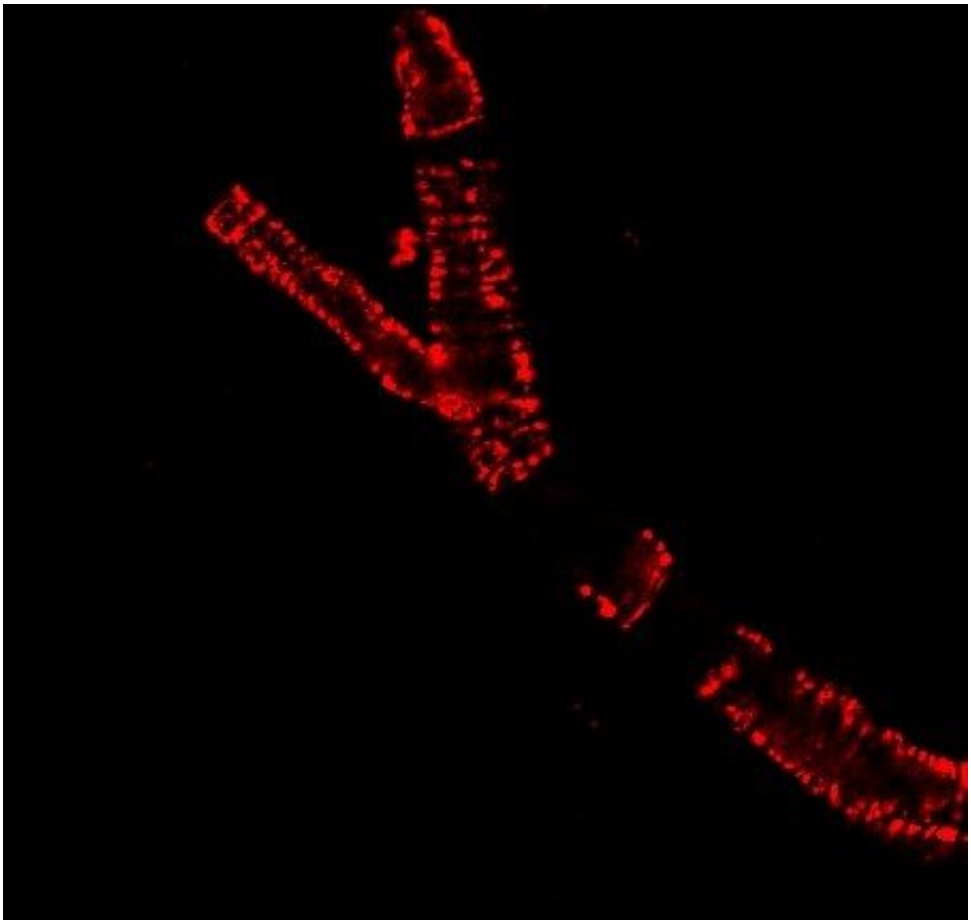

An isolated cerebral arteriole from a mouse model, marked by a live-cell dye. Credit: Osama Harraz, Ph.D., University of Vermont Larner College of Medicine

High blood pressure, or hypertension, is the leading modifiable risk

factor for cardiovascular diseases and premature death worldwide. And key to treating patients with conditions ranging from chest pain to stroke is understanding the intricacies of how the cells around arteries and other blood vessels work to control blood pressure. While the importance of metals like potassium and calcium in this process are known, a new discovery about a critical and underappreciated role of another metal—zinc—offers a potential new pathway for therapies to treat hypertension.

The study results were published recently in *Nature Communications*.

All the body's functions depend on arteries channeling oxygen-rich blood —energy—to where it's needed, and smooth muscle cells within these vessels direct how fast or slow the blood gets to each destination. As smooth muscles contract, they narrow the artery and increase the blood pressure, and as the muscle relaxes, the artery expands and blood pressure falls. If the blood pressure is too low the blood flow will not be enough to sustain a person's body with oxygen and nutrients. If the blood pressure is too high, the blood vessels risk being damaged or even ruptured.

"Fundamental discoveries going back more than 60 years have established that the levels of the calcium and potassium in the muscle surrounding blood vessels control how they expand and contract," say lead author Ashenafi Betrie, Ph.D., and senior authors Scott Ayton, Ph.D., and Christine Wright, Ph.D., of the Florey Institute of Neuroscience and Mental Health and The University of Melbourne in Australia.

Specifically, the researchers explain, potassium regulates calcium in the muscle, and calcium is known to be responsible for causing the narrowing of the arteries and veins that elevate blood pressure and restrict blood flow. Other cells that surround the blood vessel, including

endothelial cells and sensory nerves, also regulate the calcium and potassium within the muscle of the artery, and are themselves regulated by the levels of these metals contained within them.

"Our discovery that zinc is also important was serendipitous because we'd been researching the brain, not blood pressure," says Betrie. "We were investigating the impact of zinc-based drugs on brain function in Alzheimer's disease when we noticed a pronounced and unexpected decrease in blood pressure in mouse models treated with the drugs."

In collaboration with researchers at the University of Vermont's Larner College of Medicine in the United States and TEDA International Cardiovascular Hospital in China, the investigators learned that coordinated action by zinc within sensory nerves, endothelial cells and the muscle of arteries triggers lower calcium levels in the muscle of the blood vessel. This makes the vessel relax, decreasing blood pressure and increasing blood flow. The scientists found that blood vessels in the brain and the heart were more sensitive to zinc than blood vessels in other areas of the body—an observation that warrants further research.

"Essentially, zinc has the opposite effect to calcium on blood flow and pressure," says Ayton. "Zinc is an important metal ion in biology and, given that calcium and potassium are famous for controlling blood flow and pressure, it's surprising that the role of zinc hasn't previously been appreciated."

Another surprising fact is that genes that control zinc levels within cells are known to be associated with cardiovascular diseases including hypertension, and hypertension is also a known side effect of zinc deficiency. This new research provides explanations for these previously known associations.

"While there are a range of existing drugs that are available to lower

blood pressure, many people develop resistance to them," says Wright, who added that a number of cardiovascular diseases, including pulmonary hypertension, are poorly treated by currently available therapies. "New zinc-based blood pressure drugs would be a huge outcome for an accidental discovery, reminding us that in research, it isn't just about looking for something specific, but also about just looking."

More information: Ashenafi H. Betrie et al, Zinc drives vasorelaxation by acting in sensory nerves, endothelium and smooth muscle, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23198-6

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