

# Link identified between age, cardiovascular disease

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Researchers in the Linus Pauling Institute at Oregon State University have discovered a fundamental mechanism that causes aging blood vessels to lose their elasticity – a literal "hardening of the arteries" that is often a prelude to high blood pressure and cardiovascular disease.

An understanding of this mechanism, scientists say, provides an important new target for both drugs and dietary changes that might help prevent or treat atherosclerosis and heart disease. This is a leading cause of death around the world that, in some form, affects about 80 percent of older Americans.

The findings were just published in *Aging Cell*, a professional journal. The study was funded by the National Institute on Aging, National Center for Complementary and Alternative Medicine, and the American Heart Association.

"This could ultimately provide a new, fundamental and possibly inexpensive way to treat or prevent high blood pressure," said Tory Hagen, an OSU associate professor of biochemistry and biophysics, and lead author on the study. "It's also a key to understanding the biological effects of inflammation, which increasingly seems to be implicated not only in heart disease but other chronic and neurologic diseases."

The research, which was done in test tubes and animal models, needs to be confirmed in humans before it could form the basis for new therapies. But the fundamental findings reveal an important insight into

how blood vessels change with age and lose much of their ability to relax, contract, and facilitate the circulation of blood in the body.

Blood vessels in humans, like those of other animals, have vascular "smooth muscles" that can alternatively relax and contract to accommodate fluctuations in blood flow and volume. A thin layer of "endothelial cells" in the vessels serves, in part, as a sensor mechanism to help regulate this process. And proper function of the endothelial cells, in turn, is driven by specific enzymes and signaling pathways.

What has been known for some time is that blood vessels, as they age, lose much of their capacity to relax – according to the OSU research, about half of that capacity, even in healthy vessels. If the vessels are narrowed by atherosclerotic lesions the problem is further exacerbated. High blood pressure is often the result, which in turn can lead to heart attacks, strokes, and death.

Some of the most common high blood pressure medications, in fact, function by helping to address this loss of elasticity in blood vessels. The nitroglycerin pills used by many people with unstable angina provide an immediate boost of nitric oxide, which serves to relax blood vessels.

What has not been known is exactly why this "hardening" of the blood vessels occurs with age. The new OSU study answers much of that question. "Basically, we've learned that in older blood vessels, the cellular signaling process is breaking down," said Hagen. "The vessels still have the ability to relax much as they did when they were younger, but they are not getting the message."

A complex enzymatic process outlined in the new study explains how this "failure to communicate" occurs. An enzymatic reaction called "phosphorylation," which is essential to the signaling process, loses about half of its effectiveness in aging blood vessels. This loss of

phosphorylation is due to less activity in one enzyme, AKT, that facilitates the process, and excess activity of phosphatases, that reverse it.

The researchers also discovered that ceramides, one type of lipid, or fat, are primarily responsible for the excessive activity of phosphatases. And in laboratory experiments with blood vessels from rats, they were able to inhibit ceramide synthesis.

"The laboratory studies were very compelling," Hagen said. "We were able to make aging blood vessels behave as if they were young again."

According to Balz Frei, professor and director of the Linus Pauling Institute, and co-author on this study, a strength of this approach is that it points the way to use diet to prevent the decline in blood vessel function with age, and to treat it, if necessary, through drugs.

"A compound we're already using showed the ability to lower ceramide levels and improve the cell signaling process, and this compound would be a good starting point for possible drug therapies," Hagen said. "And certain types of diet may help reduce this natural, age-related process."

As is appropriate for many other disease concerns and health conditions, Frei said, a diet that's heavy in fruits and vegetables seems to slow down the loss of blood vessel function. However, the scientists also are doing research with lipoic acid, a powerful antioxidant, that is very promising and may ultimately show it could play a role as a dietary supplement to help address this problem.

This overall process, the researchers said, is linked to a low-grade, chronic inflammation that occurs with aging, in blood vessels and probably many other metabolic functions. Efforts to understand and address these inflammatory processes are some of the most promising

areas of chronic disease prevention and treatment, they said.

Source: Oregon State University

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