High Blood Pressure In Older Adults Traced To Gene's Effects In Blood Vessels

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Scientists have identified the gene that sets off a sequence of events in the blood vessels of otherwise healthy adults that can lead to high blood pressure. The disease process eventually makes conditions in vessels ripe for the creation of blockages that can cause heart attacks, strokes and circulatory problems.

The finding in a study led by Ohio State University researchers might lead to new therapeutic options for high blood pressure, especially hypertension associated with aging. Obesity and aging contribute to increasing cases of high blood pressure, which currently affects an estimated 50 million Americans.

Despite more intensive treatments available for hypertension, little has been done to prevent it. A change in the structure of the blood vessels, called vascular remodeling, increases with age and triggers the onset of the disease. When remodeling occurs, blood vessel walls increase in thickness, decreasing the diameter of the channel through which blood normally flows.

The gene, called profilin 1, has been traced to a series of interactions within the smooth muscle cells of blood vessels that causes those cells to increase in size. This in turn narrows the channel through which blood flows, causing stress on vessel walls, injuring the lining of the vessel walls and making it easier for blockages to develop. By identifying this pathway, researchers hope to pinpoint the most effective therapeutic target to interfere with the disease process.

The researchers used genetically altered mice that produce excessive amounts of the human profilin 1 gene in the vascular smooth muscle cells and observed the changes to the vessels that followed, which led to high blood pressure by the time the mice were 6 months old – the rough equivalent to middle age in humans.

“We created the disease in the animals and then went backwards to understand how the disease developed. This is an important finding because vascular disease originates in the smooth muscle cells, which have significant impact on the dysregulation of blood pressure that leads to heart disease,” said Hamdy Hassanain, assistant professor of anesthesiology at Ohio State University and senior author of the study. Hassanain also is an investigator in Ohio State's Davis Heart and Lung Research Institute.

The findings were published in the Dec. 28, 2007 issue of the *Journal of Biological Chemistry*.

Blood vessels contain three important layers – the endothelium that lines the vessel walls, the smooth muscle cells responsible for regulating blood flow, and the lumen, the open channel through which blood travels. In healthy young humans, the production of compounds by the cells in these layers remains balanced, allowing for normal vessel function and unrestricted blood flow.

Hassanain developed a transgenic mouse that produces excess human profilin 1 in the smooth muscle cell area with the intent to cause stress in the vessel walls that leads to hypertrophy, or an enlargement of the smooth muscle cells that eventually leads to structural and functional changes in the entire vessel. The mice were developed to test the theory that the impaired regulation of the profilin 1 gene would eventually lead to high blood pressure, and observe how that happens.

“Vascular remodeling is a known problem as people get older. Their blood vessels tend to stiffen, even in healthy adults. This causes stress on the vessels, which leads to hypertension,” Hassanain said.

At the heart of the vessel activities is a protein called actin within the smooth muscle cells, and its relationship to profilin 1. In the presence of too much profilin1, actin is transformed from a loosely configured protein into a more rigid fibrous state. This change in actin's nature increases the size and the stiffness of smooth muscle cells.

The cells undergo other changes that prepare them for cell division, but under these conditions, the vessel lining releases a substance, nitric oxide, that won't allow the cells to divide. The smooth muscle cells' resulting growth pushes inward, putting pressure on the lumen and restricting blood flow, resulting in high blood pressure.

“Profilin 1 is a tool that triggers events that make the vessel more constricted and leads to the signal that results in vascular remodeling. Because we have understood the pathway of the disease process, we might be able to control vascular remodeling,” Hassanain said.

Once a vessel is remodeled, more trouble is typically ahead. Diseased vessels are often characterized by injuries to the endothelium, where the lining of the vessel loses its protective layer. Once the lining is injured and vulnerable, smooth muscle cells will start to migrate inward, creating sticking points for fats, debris and other blood remnants.

“That's the first hint of plaque. The smooth muscle cell migration is the tip of the iceberg of the plaque,” Hassanain said. “We're talking about all vessels, but when we're talking about this narrowing effect in the brain, this could lead to stroke, and in the coronary artery, it could lead to heart attack. It's all the same phenomenon.”

Source: Ohio State University