New evidence of how high glucose damages blood vessels could lead to new treatments

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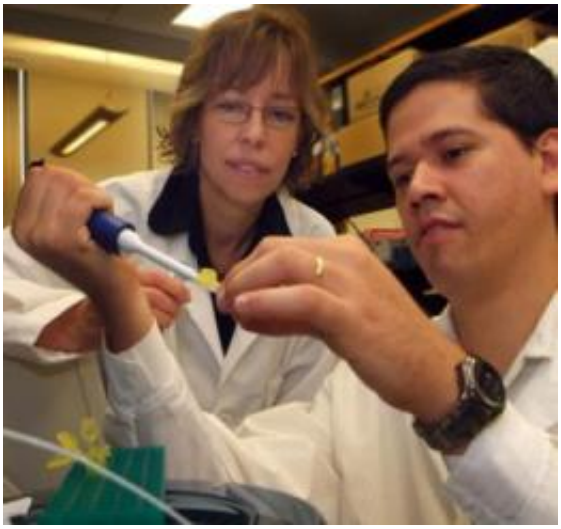

This is Dr. Rita C.Tostes, physiologist in the MCG School of Medicine and Victor Lima, a graduate student at the University of Sao Paulo. Credit: Medical College of Georgia

New evidence of how the elevated glucose levels that occur in diabetes damage blood vessels may lead to novel strategies for blocking the destruction, Medical College of Georgia researchers say.

They found a decreased ability of blood vessels to relax resulted from increased activity of a natural mechanism for altering protein form and function, says Dr. Rita C.Tostes, physiologist in the MCG School of Medicine.

The researchers suspect increased modification of proteins by a glucose-derived molecule is a player in vascular problems associated with hypertension, stroke and obesity as well.

One aftermath of high glucose levels is low levels of the powerful vasodilator nitric oxide in blood vessels, a shortfall that increases the risk of high blood pressure and eventual narrowing of the vessels, researchers reported at the American Society of Hypertension 24th Annual Scientific Program in San Francisco during a joint session with the Council for High Blood Pressure.

"We know diabetes is a major risk factor for cardiovascular disease and we think this is one of the reasons," Dr. Tostes says.

Diabetes increases the risk of cardiovascular disease such as heart disease and stroke, even when glucose, or blood sugar, levels are under control. In fact, about 75 percent of people with diabetes die from some form of heart or blood vessel disease, according to the American Heart Association.

Most of the glucose in the body goes directly into cells where it's modified to produce the energy source ATP. However about 5 percent of all glucose is converted to another sugar moiety, O-GlcNAc, one of the sugar types that can modify proteins.

Inside the blood vessel walls of healthy mice, MCG researchers found increased activity by O-GlcNAc competes with another mechanism for modifying proteins called phosphorylation. In blood vessels, phorphorylation modifies the enzyme that produces nitric oxide, called nitric oxide synthase, so that it makes more of the blood vessel dilator. But add more O-GlcNAc to the mix and it seems to beat phosphorylation to the punch so there is the opposite result. The longer O-GlcNAc levels were high, the worse the resulting problem, says Victor Lima, a graduate

student at the University of Sao Paulo working with Dr. Tostes.

An animal model of hypertension seemed to confirm the finding that the more O-GlcNAc, the more blood vessels contract because these animals had higher O-GlcNAc levels. "Now we are trying to see why this is happening and what comes first. Is increased blood pressure leading to changed O-GlcNAc or are augmented levels of O-GlcNAc contributing to the change we see in the vasculature of hypertensives?" Dr. Tostes says. "If we know how this changes vascular function, we can understand some of the dysfunction that we see in diabetes."

To make sure they were targeting the O-GlcNAc sugar and not dealing with other effects of glucose on blood vessels, the researchers blocked the enzyme OGA, an enzyme that normally removes O-GlcNAc from proteins so they can revert to their normal state.

If the findings continue to hold true, drugs similar to those they use in the lab to inhibit OGA or OGT, the enzyme that adds O-GlcNAc to the protein, could one day help reduce the significant cardiovascular risk associated with diabetes, Mr. Lima says. "I think it looks very promising," Dr. Tostes adds.

Future studies will include blocking the pathway for adding O-GlcNAc in hypertensive animals to study the impact on blood pressure and vascular function.

Source: Medical College of Georgia