A single mechanism for hypertension, insulin resistance and immune suppression

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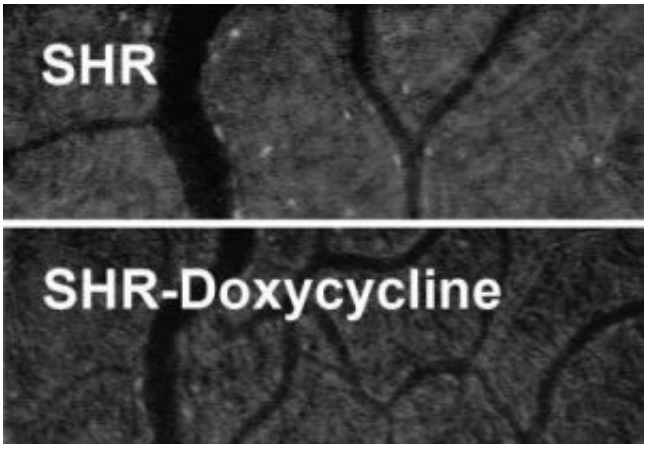

These fluorescent microscopic images of tissue taken from spontaneously hypertensive rats reveal activity of proteases MMP-1 and MMP-9 as bright spots. The lower image shows tissue from an SHR animal that had been made healthy by treatment with doxycycline, a protease inhibitor. Credit: UC San Diego Jacobs School of Engineering

Many of the 75 million Americans with essential hypertension also develop diabetes and other complications in addition to their high blood pressure, and researchers have discovered a common molecular mechanism in a strain of rat that explains why such metabolic disorders arise together in mammals.

The bioengineering researchers at UC San Diego's Jacobs School of Engineering also showed that a drug developed for unrelated purposes in

humans was effective in counteracting the underlying molecular mechanism in the spontaneously hypertensive rat (SHR), a strain predisposed to develop high blood pressure.

In a paper published June 30 in the online version of *Hypertension*, Frank DeLano, a research scientist at UC San Diego, and Geert Schmid-Schönbein, a professor of bioengineering, describe how they successfully reversed the SHR animals' symptoms of high blood pressure, a pre-diabetes condition called insulin resistance, and immune suppression.

H. Glenn Bohlen, a professor in the Department of Cellular and Integrative Physiology at Indiana University Medical School, wrote in an accompanying editorial in Hypertension that the new study will likely be important to people suffering from obesity as well as hypertension. "With the national and international emphasis on obesity and its attendant cardiovascular problems, there is a tendency to forget that essential hypertension affects about the same percentage of humans as does serious obesity and an even higher percentage of the population than does type 2 diabetes mellitus," wrote Bohlen. "The elegant study by Delano and Schmid-Schönbein points to a potentially very important overlap of an insulin resistance mechanism with hypertension in the spontaneously hypertensive rat (SHR)."

The SHR strain is a model for essential hypertension in humans because both the rodent and many humans with hypertension also develop a variety of other metabolic complications when high blood pressure strikes.

In the circulation of SHR rodents, Schmid-Schönbein and DeLano found significant levels of proteases, which are enzymes that break down proteins. Natural enzyme inhibitors found in normal healthy rats did not lower the level of protease activity in the SHR strain to normal levels.

“We were looking for a common cause of diverse but concurrent metabolic problems and we were testing our theory that enhanced proteolytic activity in the circulation may be the root cause,” said Schmid-Schönbein. “In the hypertensive rat we studied, enzymes cleave extracellular portions of several protein receptors, such as the insulin receptor, so that insulin can no longer bind and facilitate normal metabolism of glucose.”

Under normal conditions, the pancreas releases insulin in the bloodstream. The molecule then binds to insulin receptors on the cell-surface membrane, which signals the cells to absorb glucose, a main source of cellular energy. However, when a cell loses the binding site for insulin on the insulin receptors, it becomes “resistant,” or unresponsive to insulin and no longer absorbs glucose in healthy amounts on cue, which is the problem in type 2 diabetes.

The researchers showed that the SHR animals have protease activity in their circulation that cleaves more than just insulin receptors. In these animals, proteases also cleave significant numbers of CD18, an important binding receptor on the surface of infection-fighting leukocytes. CD18 gives these cells the ability to adhere to the walls of blood vessels as a way to home in on infections. With the loss of CD18 receptors, leukocytes of the SHR animals are unable to bind to the wall of blood vessels, resulting in a compromised immune system.

“These results point to a single mechanism that explains multiple and diverse cell dysfunctions encountered in hypertensive rats, and they also suggest that a similar mechanism may be operating in humans suffering simultaneously from hypertension, diabetes, and other metabolic conditions,” said Schmid-Schönbein.

The team went on to test whether administration of a protease-blocking drug could reverse the multiple metabolic complications in the rat strain.

They administered doxycycline, a seemingly unlikely candidate to have such a beneficial effect. Infectious disease specialists often prescribe doxycycline, an antibiotic, to counter bacterial infections. However, in laboratory tests doxycycline also blocks the activity of certain proteases in the SHR strain of rat.

The researchers found that protein receptors on the surface of SHR cells become clipped off as the animals develop hypertension. They used a novel visualization technique to show that after several weeks of ingesting doxycycline in their drinking water, the SHR rats developed cells that again bristled with normal CD18 and insulin receptors. The animals' metabolic conditions simultaneously improved; blood pressure normalized and symptoms of immune suppression disappeared.

"These studies indicate the first time that hypertension and cell dysfunctions associated with the metabolic syndrome may be part of an enzymatic auto-digestion process in which proteases in our body become uncontrolled and break down proteins," Schmid-Schönbein said. "Our observations provide a conceptual framework in which we can start to understand how diverse complications in the metabolic syndrome arise."

Schmid-Schönbein said his findings will likely spark follow-up studies of this mechanism in humans.

"Even if future studies only support the clear linkage of hypertension to insulin receptor cleavage in the current study of SHRs, this observation should lead to many studies of how these two problems perhaps interact," wrote Bohlen in the Hypertension editorial. "To what extent this interaction is part of the cause or consequences of mechanisms associated with hypertension will remain controversial for some time to come. However, it is tempting to speculate that treatment of hypertension may be inadvertently improving insulin sensitivity and likely many other abnormalities associated with cell surface receptors

that have been unknowingly damaged by protease activation associated with elevated blood pressure."

Source: University of California - San Diego