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## Scientists Breed Special Rats to Learn More about Hypertension, Heart Disease and Estrogen

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WINSTON-SALEM, N.C. – Scientists at Wake Forest University School of Medicine have created a better research rat – the first to enable them to study how declining estrogen after menopause can affect hypertension, heart failure and kidney damage.

“By changing a single gene that is involved in hypertension, varying effects were revealed that we never expected,” said Mark Chappell, Ph.D., senior researcher in the Hypertension and Vascular Disease Center. “These rats will allow us to study salt-sensitivity in hypertension as well as explore how estrogen depletion affects several body systems. And this is just the tip of the iceberg. We’re just starting to discover what this animal model can teach us.”

Chappell and colleagues are presenting three reports on their research this week at the American Heart Association’s 59th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research in association with the Council on the Kidney in Cardiovascular Disease. The meeting is in Washington, D.C.

“These projects suggest that estrogen may be protective, not only in renal function and development of hypertension, but in heart function,” said Chappell. “Next, we will look at different therapies, including different formulations of estrogen that may lack some of the deleterious effects associated with estrogen therapy.”

In a study led by Leanne Groban, M.D., an associate professor of cardiac anesthesia, the team looked at how estrogen depletion affects diastolic dysfunction. In this common form of heart failure, the heart muscle becomes stiff and cannot fill with enough blood to meet the body’s demands. Diastolic dysfunction is more common in women after menopause and is frequently associated with hypertension.

In these rats, the researchers found that estrogen depletion exacerbates the progression of diastolic dysfunction. Scientists have long known that estrogen helps protect heart vessels from atherosclerosis, the buildup of fatty deposits that can cause heart attacks. This research suggests that it may also protect heart function.

“Estrogen seems to exert protective actions on heart performance that may be independent from any changes in blood pressure,” said Groban.

Chappell led a project to determine if estrogen is also protective against the hypertension and renal damage that arises from excess salt in the diet. In the rats fed a high salt diet, estrogen depletion increased blood pressure and exacerbated renal injury. The lack of estrogen resulted in increase levels of a hormone called aldosterone that may contribute to both diastolic dysfunction and kidney injury.

“This seems to go hand in hand with studies published recently showing that blocking aldosterone is protective to the heart and kidneys irrespective of its effects on blood pressure,” said Chappell, an associate professor in the School of Medicine, which is part of Wake Forest University Baptist Medical Center.

In the third project, the scientists found that estrogen depletion results in marked increases in blood pressure, which they hope will help them understand why a woman’s chances of getting high blood pressure increase considerably after menopause. Led by Liliya Yamaleyeva, M.D., the researchers measured nitric oxide, a hormone

that has been found to relax blood vessels and lower blood pressure.

Three different enzymes are involved in nitric oxide formation and the researchers found that estrogen depletion augments one of the enzymes, but markedly reduces one of the others.

“We conclude that one of the nitric oxide enzymes may be an important mechanism that causes blood pressure to increase after estrogen depletion,” said Yamaleyeva.

The development of an animal that is sensitive to estrogen’s effects is significant because most human and animal hypertension research has focused on males. The rats are also sensitive to salt, which will help the researchers work to learn more about how salt intake affects blood pressure in both men and women.

“We’ll see if there are differences between males and females in how they respond to treatments and whether they are salt-sensitive,” said Chappell. “About half of people with hypertension have increased pressure when they consume high levels of salt and we don’t know why.”

This research is funded by National Heart, Lung, and Blood Institute and the American Heart Association. The new strain of so-called “designer” rats are created by transferring one or several specific genes of interest to a recipient rat and allows scientists to better learn how genes may work together to cause cardiovascular disease in humans.

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**Media Contacts: Karen Richardson, [krchrdsn@wfubmc.edu](mailto:krchrdsn@wfubmc.edu); Shannon Koontz, [shkoontz@wfubmc.edu](mailto:shkoontz@wfubmc.edu); at 336-716-4587**

**Wake Forest University Baptist Medical Center** is an academic health system comprised of North Carolina Baptist Hospital and Wake Forest University Health Sciences, which operates the university’s School of Medicine. The system comprises 1,187 acute care, psychiatric, rehabilitation and long-term care beds and is consistently ranked as one of “America’s Best Hospitals” by *U.S. News & World Report*.

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