New study unravels why common blood pressure medicine can fail

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Every year, more than 120 million prescriptions are written worldwide for thiazide drugs, a group of salt-lowering medicines used to treat high blood pressure. These drugs are often work very well, and over decades have saved hundreds of thousands of lives.

But in some patients, thiazides are not effective; in others they lower blood pressure for a while and then stop working. The reasons for this have remained a mystery. Now, a new study by researchers at the University of Maryland School of Medicine (UM SOM) has revealed a key mechanism for this failure.

Paul Welling, MD, a professor of physiology at the school, and his post-doctoral fellow, P. Rick Grimm, PhD, found the specific genes and

pathways used by the kidneys to compensate for thiazides' activity. The paper was published in the latest issue of the journal *Journal of Clinical Investigation*. The research was done in conjunction with scientists at Vanderbilt University and Emory University.

"This is the first time we really understand how this process works," said Dr. Welling, an expert on potassium and sodium balance, kidney disease and hypertension. "It's as if the kidney knows that it's losing too much salt and activates mechanisms to retain salt in other ways."

Thiazides work by inhibiting the movement of salt through the kidney, causing the kidneys to expel salt and water. Salt often raises blood pressure by increasing the amount of water in the vascular system; over time, this fluid puts pressure on the heart and blood vessels, and can cause hypertension. The kidney counteracts the drugs' effect by retaining more salt, keeping blood pressure high.

Dr. Welling and his collaborators studied an animal model that was genetically engineered to inhibit salt retention, mimicking the effect of thiazides. Using sophisticated technology to track genetic changes in these animals, they found that nearly 400 key genes change their activity to help regulate how the kidneys handle salt. Once activated, these genes worked together, acting on three different pathways related to salt retention. In short these genes increased the body's ability to hold onto salt, shedding light on how the system can react to thiazides. The interaction of these genes and pathways had not been elucidated in detail before.

The new work has important implications and reveals new possibilities for patients with high blood pressure. Dr. Welling says it may now be possible to begin developing drugs that affect the mechanisms through which the body counteracts thiazides. These drugs might eventually be used alongside thiazides, or might be used on their own.

In addition, the researchers have identified a molecule that increases in the urine when the kidney is working to counteract thiazides. Dr. Welling and his colleagues are now investigating the possibility of using this molecule as a "biomarker," allowing doctors to quickly and easily detect when thiazides won't work, or have stopped working, in a particular patient.

"This new work by Dr. Welling is a powerful example of the strong links between basic research and clinical results," said Dean E. Albert Reece, MD, PhD, MBA, who is also the vice president for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean of the School of Medicine. "Now that we know more about these novel pathways and processes, we can begin to find new ways to help patients with high blood pressure."

Provided by University of Maryland

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