New class of molecules may help prevent fatal complication in patients with kidney disease

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Researchers at the University of Maryland School of Medicine have made an important discovery about why potassium builds up to dangerous levels in the bloodstream, a relatively common medical problem that affects about eight percent of hospitalized patients. They have identified a new molecular pathway and a new class of molecules responsible for preventing potassium from being excreted normally through the kidney. Their study was just published in the *Journal of Clinical Investigation*.

The researchers hope that their discovery will lead to the development of a new class of drugs to treat the condition, known as hyperkalemia, which is caused when patients can't properly excrete excess potassium. If it is not treated promptly, it can cause fatal cardiac arrest.

"We are particularly excited about the translational potential of our basic science discovery," says Paul A. Welling, M.D. professor of physiology at the University of Maryland School of Medicine. "Currently, there are no drugs that specifically target the molecular defect in kidney potassium retention. This new class of drugs will pave the way to allow damaged kidneys from long-standing high blood pressure, diabetes or heart disease, to continue to properly excrete potassium in the urine, so that potentially fatal hyperkalemia can be prevented."

Potassium is critical for proper functioning of muscles, nerves and the heart. The kidney is the organ primarily responsible for eliminating excess potassium if too much of it accumulates in the blood stream.

People at highest risk for abnormally high levels of potassium in the blood are those with kidney disease because they cannot properly excrete the potassium through the urine. About 67 percent of cases of severe hyperkalemia are fatal if they are not caught and treated promptly.

A kidney gene called ROMK (Renal Outer Medullary K+ Channel) controls the levels of potassium excretion in the kidney. In people with kidney disease, the protein made by this gene no longer signals properly to ensure adequate excretion through the urine, so the potassium can build up in the blood. With funding from the National Institute of Diabetes and Digestive and Kidney Disease at the National Institutes of Health, Dr. Welling, and his post doctorate fellow, Liang Fang, Ph.D. have discovered this new class of protein molecules responsible for this abnormal signaling. This new molecule has been shown to interact with the ROMK gene and then inhibit the excretion of potassium, thus causing high blood levels.

"Our findings solve a mystery of how potassium excretion is turned off in response to dietary potassium deficiency and points to an underlying defect in kidney disease" says Dr. Fang. The name of this new adaptor protein is called ARH (Autosomal Recessive Hypercholesterolemia protein). The researchers hope that now that this pathway has been uncovered, it will lead to the development of new drugs that can prevent ARH from interacting with the ROMK gene.

E. Albert Reece, MD, PhD, MBA, Vice President for Medical Affairs, University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine, says these findings change our basic understanding of how potassium balance is maintained in the body and is critical in the care of patients with kidney disease from conditions such as diabetes. He adds, "Dr. Welling's discovery provides a completely new road map to develop therapeutic interventions for this relatively common, but very serious,

complication of kidney disease. This type of basic science research will translate into important clinical therapies for patient care in the future."

Source: University of Maryland Medical Center