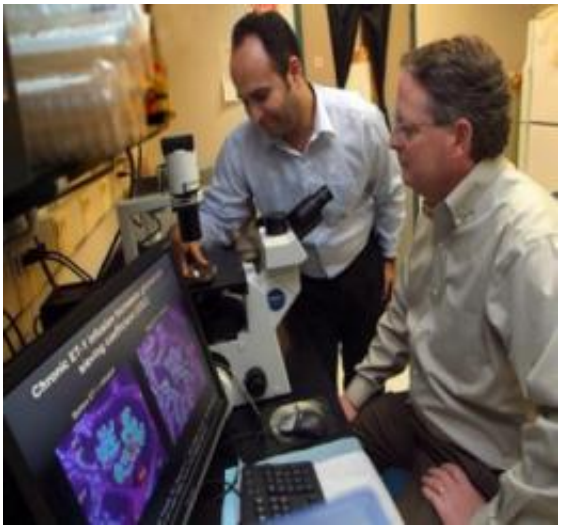
Scientists learn more about how kidneys fail and how new drugs may intervene

November 16 2010



Graduate student Mohamed A. Saleh (left) and Dr. David Pollock have research published in *Hypertension* that helps explain how protein gets in the urine when the kidneys begin to fail and how a new drug may block it. Credit: Phil Jones

Scientists are learning more about how protein gets in the urine when the kidneys begin to fail and how a new drug blocks it.

"We have known for a long time that renal failure comes with protein in your urine, especially in diabetes," said Dr. David Pollock, renal physiologist at the Medical College of Georgia Vascular Biology Center. It's also known that a new class of drugs called endothelin A receptor antagonists reduce protein in the urine.

New research published in the journal *Hypertension* connects the two, providing more information about how new drugs under study for kidney failure work.

The scientists have shown in rats that increased levels of the peptide endothelin 1 – characteristic of conditions such as diabetes and high-salt diets – increase the permeability of tiny kidney filters. The filters recycle key components such as red and white blood cells and proteins, including albumin, that help keep blood vessels from leaking fluid.

The increased permeability causes the proteins to be eliminated in the urine, resulting in a double whammy that likely includes generalized body swelling and further kidney damage. "Without albumin, the fluid just goes into your tissue," Pollock said.

"This filter, which is like cheesecloth, gets damaged in kidney failure and so you get more of these proteins in your urine. Filters start scarring over, you lose the nephron (the filter and its associated kidney cells) and so the kidneys slowly die," he said.

And that's just part of the damage. High endothelin levels also trigger inflammation, sending out proinflammatory molecules that attract inflammatory cells like white blood cells and macrophages to the kidneys, MCG researchers have shown. They also have shown that endothelin A receptor antagonists reduce this inflammatory response.

"There has been no drug that really targets diabetic nephropathy," said Mohamed A. Saleh, MCG graduate student and the study's first author. The study provides more scientific evidence that the new endothelin A receptor antagonists may be the first class of drugs to fit that bill, said Saleh, noting that his native Egypt, like the United States, has an increasing problem with diabetes.

The positive results were achieved without affecting blood pressure, the scientists noted. Endothelin receptor antagonists are known to have health benefit but precisely why was an unknown, said Pollock, corresponding author on the study. "A lot of people thought they just lower blood pressure and anything that lowers blood pressure is going to make your kidneys feel better," he said.

Endothelin 1 has A and B receptors and whether the peptide hurts or helps generally depends on which receptor it activates. The B receptor is considered the good guy, helping the kidney eliminate excess sodium, for example. The A receptor is generally considered a trouble maker that interferes with sodium excretion, constricts blood vessels and promotes inflammation.

The MCG scientists want to compare A inhibitors to another new class of drugs that blocks both the A and B receptors.

Provided by Medical College of Georgia