Hypertension researcher encourages colleagues to expand their focus

September 14 2013

Dr. David Pollock has a simple message for fellow hypertension researchers: think endothelin.

In a country where better than 30 percent of adults have high blood pressure and 50-75 percent of those have salt-sensitive hypertension, he believes the powerful endothelin system, which helps the body eliminate salt, should not be essentially ignored.

However, the research and clinical world focus on suppressing a better-known system, which prompts the body to hold onto salt, said Pollock, Chief of the Section of Experimental Medicine at the Medical College of Georgia at Georgia Regents University.

Pollock is giving the 2013 Lewis K. Dahl Memorial Lecture Sept. 14 during the American Heart Association's High Blood Pressure Research 2013 Scientific Sessions in New Orleans.

"If you look at blood pressure regulation and salt-controlled sodium excretion, everybody sees the renin-angiotensin-aldosterone system. That is what the books say." Pollock said. No doubt the system is important. When blood volume is low, the kidneys secret renin to make the hormone angiotensin. Angiotensin drives blood pressure up by promoting sodium retention directly and by stimulating release of aldosterone, a hormone that prompts the kidneys to resorb sodium rather than eliminate it in the urine.

It's a protective system intended to ensure that the body has enough sodium to keep blood pressure at sufficient levels to sustain life. It's also a system that's somehow dysregulated in some hypertensive patients who take ACE inhibitors or angiotensin receptor blockers to turn it down.

Since most Americans already turn down this system by eating too much salt, Pollock argues that enhancing sodium excretion might be a better approach, particularly for those not responding to existing therapies.

In fact, when an animal on a high-salt diet is given a drug to block endothelin's B receptor, blood pressure goes up 50 points, Pollock said. He regularly reminds research colleagues that blocking angiotensin receptors won't produce nearly such dramatic results. In fact, he thinks problems with the endothelin system – possibly resulting from a developmental defect or high-salt exposure early in life – may help explain why some folks who eat a high-sodium diet get high blood pressure and others don't. But this leads to one of the weak points of endothelin and probably part of the reason it's not been top of mind for hypertension researchers, he said.

When the salt-eliminating B receptor is inactive for whatever reason, endothelin's A receptor, which actually constricts blood vessels, gets activated so blood pressure goes up, Pollock said. An interesting aside is that, at least in the short term, higher blood pressure makes it easier for the kidneys to eliminate sodium without the help of the B receptor.

Endothelin was labeled the most potent vasoconstrictor ever described when it was first purified in the late 1980s, but it was a long time before there was any attention paid to the diametrically opposed actions of the B receptors, Pollock said. Receptor antagonists didn't exist in those early days anyway and efforts to block endothelin synthesis didn't work well because there were so many forms of the enzyme that make endothelin scattered throughout the body, he said.

While still working for a pharmaceutical company, Pollock helped develop on one of the first A receptor antagonists that's now in the final stage of clinical trials for chronic kidney disease. Since the early patents on the endothelin-blocking drugs are about to run out, it's unlikely that new drug development dollars will be in the offing, Pollock said. The good news is that drugs already in use for pulmonary hypertension, which shut down the A receptors, likely have crossover potential for salt-sensitive hypertension, Pollock said.

Pollock's studies have shown that the kidney's endothelin B receptor plays a critical role in eliminating both acute and chronic salt loads by activating nitric oxide, a potent dilator of blood vessels, in the kidneys. In fact, the kidneys make more endothelin than any place in the body.

"We had no idea it was going to be this important in salt regulation," Pollock said. "The main point I want to make is that people studying hypertension, salt-sensitivity particularly, need to consider what is happening to the endothelin system when they are doing their research. There are only a handful of us who have been studying it with any real intensity."

Key questions include how the B receptor gets turned off. Interestingly, researchers already know that the angiotensin system shuts the receptor down when patients are on a low-salt diet. Do hypertensive patients on a low-salt diet also have their B receptors turned off? "It's a good question and another reason that targeting the renin-angiotensin-aldosterone system may not give you the whole answer," Pollock said.

The Lewis K. Dahl Memorial Lecture was established in 1988 by the Council for High Blood Pressure Research in honor of Dahl's pioneering work on the relations between salt, the kidney and hypertension, and for establishing the Dahl salt-sensitive rat, a major genetically based experimental model of hypertension. Pollock has been a fellow of the

council since 2000.

Provided by Medical College of Georgia