Better understanding of blood vessel constrictor needed to harness its power for patients

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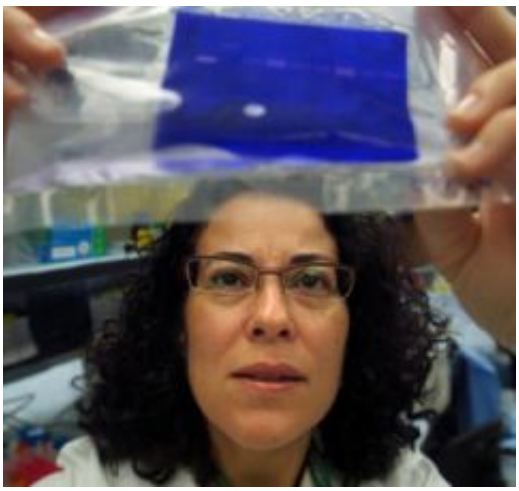

Dr. Adviye Ergul, physiologist in the MCG Schools of Medicine and Graduate Studies. Credit: Medical College of Georgia

To harness endothelin-1's power to constrict blood vessels and help patients manage high blood pressure or heart failure, scientists must learn more about how endothelin functions naturally and in disease states, says a Medical College of Georgia researcher.

Despite strong laboratory evidence that blocking endothelin-1 receptors would be an effective, targeted therapy for these two major health problems, the drugs failed patients, says Dr. Adviye Ergul, physiologist

in the MCG Schools of Medicine and Graduate Studies.

"These endothelin-1 receptors are logical targets for drugs to treat hypertension because of their key role in vasoconstriction, but the targets are moving and we don't know how one target plays off another," says Dr. Ergul, who discussed novel aspects of endothelin receptor interaction during the 62nd High Blood Pressure Research Conference and Workshop in Atlanta.

"The current thinking in pharmacology is one hormone, one receptor equals boom: the effect. I think cells are much smarter," she says. This week, Dr. Ergul challenged colleagues across the country to consider emerging evidence that usual receptor communication is likely more complex than they thought and that disease may significantly alter communication.

Endothelin-1 receptors are known to interact: one way blood vessels keep a healthy tone, for example, is that a and b receptors on smooth muscle cells prompt constriction while b receptors on the lining of blood vessels work with nitric oxide to promote relaxation. Endothelin-1 receptors on the kidneys are a player as well, helping wring out excess water and salt. "There is a delicate balance," says Dr. Ergul.

But there's apparently more to the relationships. She holds up a handful of recent journal articles which reflect mounting evidence that receptors actively work as teams of two or more. That teamwork could change their function. New technology enables scientists to literally watch receptors move closer together on a cell surface, clearly indicating that something is going on.

"Numerous drugs have been developed that are antagonists that can block these receptors with the idea they can be used in hypertension and heart failure. In animal models, they worked well," she says. But in

clinical trials they failed badly; a drug for heart failure actually worsened problems such as labored breathing and swelling in patients already having difficulty moving blood through their body.

The first antagonists blocked both known receptors: a and b; the next generation blocked one or the other but still didn't work. A notable exception is endothelin-1 antagonists that reduce excessive pressure and tissue buildup inside the blood vessels of patients with pulmonary hypertension. In addition to constricting blood vessels, endothelin-1 can help blood vessels grow bigger but too much can result in protein deposits that stiffen blood vessel walls.

Scientists have been scratching their heads over why blocking these receptors hasn't panned out; they've even looked for an "atypical" receptor that might explain it. But Dr. Ergul, an expert on endothelin-1's role in diabetes, believes the unexpected results are better explained by poorly understood relationships in normal and disease states. "How receptors dimerize, how they get closer together on the cell surface, likely needs to affect our drug design," she says.

Source: Medical College of Georgia