Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/the-endothelin-et-system-and-its-role-in-resistant-hypertension/14225/

Released: 08/15/2022
Valid until: 08/15/2023
Time needed to complete: 1h 02m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Endothelin (ET) System and Its Role in Resistant Hypertension

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Rajagopal:
Hello, my name is Sudarshan Rajagopal and I'm at Duke University School of Medicine. This presentation is on the endothelin system and its role in resistant hypertension. The endothelin system is central to proper vascular physiology and function. In the 1970s, it was discovered that there was an endothelial-derived relaxation factor, which was later identified to be nitric oxide. Now, in the early 1980s, it was discovered that there were also endothelial-derived vasoconstrictors and then in 1987, endothelin-1 was discovered as this potent endothelial-derived vasoconstrictor. Over the past 30 years, we've learned a lot about the complex biology of this system.

As you can see here on the right, there are multiple levels of regulation at this system. There are three different endothelin peptides, endothelin-1, 2, and 3 that are generated from processing of larger precursors, the prepro and big endothelin-1, 2, and 3. Now, these three endothelin peptides bind to two different receptors, the type A and B endothelin receptors, refer to as ETA and ETB and these receptors then signal through different heterotrimeric G proteins as noted here.

Soon after their discovery, it was noted that the structure of endothelin-1 was very similar to that of a set of snake venom toxins called sarafotoxins, as you can see from this protein alignment above and indeed these sarafotoxins bind to these same endothelin receptors, leading to severe vasoconstriction and the snake that has these toxins is shown below, the Atractaspis engaddensis, also known as the Saraf Ein Gedi in Hebrew, which is commonly called the Israeli mole viper. So even nature has taken advantage of the system as a poison.

Endothelin plays a central role in the vasculature by signaling between endothelial cells and smooth muscle cells. So ET-1 was discovered as a long-lasting and extremely powerful vasoconstrictor and as you can see in this figure, ET-1 is released from the vascular endothelium, where it can bind to its own receptors, the ETB receptors, on endothelial cells or bind to both ETA and ETB receptors on smooth muscle cells and at these smooth muscle cells, ET-1 promotes vasoconstriction and smooth muscle cell proliferation. Now, interestingly, the actions of ETB and endothelial cells actually promotes the release of nitric oxide and vasodilation and antiproliferation, so this is a complex system. Of note, mice lacking ET-1 and endothelial cells are hypotensive, they have low blood pressure consistent with their central role of ET-1 in promoting high blood pressure and ET-1 overexpression also increases blood pressure. Now, other cells express these receptors, such as macrophages, and these are also thought to contribute to hypertension.

Endothelin also plays an important role in the kidney. Chronic kidney disease is associated with increased formation of ET-1, which promotes renal injury and fibrosis through ETA. As you can see, ETA is expressed in a wide range of cell types in the kidneys, in the vasculature, but also in podocytes, the renal tubules, mesangium, and in inflammatory cells. Through increased renal ET-1, acting through ETA and all these different cell types can promote chronic kidney disease and indeed there have been multiple trials of endothelin receptor antagonists in chronic kidney disease some of which have shown an improvement albuminuria in patients who are already on blockade of their renin-angiotensin-aldosterone system. Now, these drugs endothelin receptor antagonists, or ERAs for

short, block signaling through ETA as well as ETB, depending on the specific drug. They have been FDA approved in the treatment of pulmonary arterial hypertension and are now standard of care.

So PAH is a disease of the small blood vessels of the lungs, the pulmonary arterials, and it's characterized by vasoconstriction and smooth muscle cell proliferation and by blocking endothelin-1 signaling in the pulmonary vasculature, it's been shown that ERAs improve hemodynamics, six minute walk distance, and time to clinical worsening in patients with pulmonary arterial hypertension. There are some side effects, patients can have fluid retention and they can have a mild drop in hemoglobin. With their well known role in hypertension, is there a potential role for ERAs in the treatment of resistant hypertension? So this is data with the novel drug, aprocitentan, a dual ETA and B antagonist and it was studied in patients with a sitting diastolic blood pressure of 90 to 109 and what the investigators found was that aprocitentan at 10, 25, and 50 milligram doses decreased sitting systolic/diastolic, automated office blood pressure. This benefit was also seen in ambulatory blood pressure. Also notable was that a similar incidence of adverse events was seen in the aprocitentan and placebo groups.

So to summarize, endothelin-1 is one of the most potent vasoconstrictors in the human body and that an animal models decreased expression of ET-1 decreases blood pressure and increased expression of ET-1 increases blood pressure. Now, endothelin or their receptors are expressed in a wide range of cells. These include vascular cells like endothelial cells and smooth muscle cells, but also different cells in the kidney and immune cells. The endothelin system has been shown to play roles in multiple diseases, such as hypertension, chronic kidney disease, and pulmonary arterial hypertension, and now we have early clinical data that suggests a benefit of ERAs in the treatment of resistant hypertension. This suggests a novel approach to the treatment of resistant hypertension, thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.