New target for heart failure therapy identified

March 16 2009

A novel signaling pathway plays a significant role in the production of aldosterone, a hormone that promotes heart failure after a myocardial infarction, according to a study conducted by Thomas Jefferson University researchers.

The findings, which will be published online this week in Proceedings of the National Academy of Sciences, show that aldosterone production is mediated by a protein called beta-arrestin-1. Beta-arrestin-1 binds to angiotensin II receptors when they are activated by angiotensin II.

Aldosterone is secreted by the adrenal cortex. Its levels are elevated in chronic heart failure, and its presence contributes to morbidity and mortality of the disease. It contributes to heart failure progression and diminished cardiac function after myocardial infarction.

The production of aldosterone was previously thought to be solely the result of the activation of G-proteins, which are also activated when angiotensin II binds to its receptors, according to Anastasios Lymperopoulos, Ph.D., a Post-Doctoral Research Fellow in the Center for Translational Medicine and the George Zallie and Family Laboratory for Cardiovascular Gene Therapy at Jefferson Medical College of Thomas Jefferson University.

"The bottom line is that in order to effectively suppress aldosterone production, you need to inhibit beta-arrestin-1 in addition to inhibiting G-proteins," said Dr. Lymperopoulos, who is the lead author of the study.

All the drugs currently available for suppression of aldosterone by angiotensin II primarily target G-protein signaling pathways. However, Walter Koch, Ph.D., the W.W. Smith Professor of Medicine and the Director of the Center for Translational Medicine and the George Zallie and Family Laboratory for Cardiovascular Gene Therapy, said that these data clearly show that beta-arrestin1 plays a more significant role in aldosterone secretion than G-proteins.

"Aldosterone secretion is dependent on beta-arrestin-1," Dr. Koch said. "It may not be independent of G-proteins, but beta-arrestin-1 is definitely the critical player. The goal should be to find a new antagonist that can block beta-arrestin-1 and G-protein activation equally well. Doing so would lead to lower aldosterone levels at its source and alleviate negative remodeling processes in the injured heart."

Source: Thomas Jefferson University