

James & Esther King Biomedical Research Program

Smith, Layton

Department of Drug Discovery
Scripps Florida

2006 Program
New Investigator (3-year project)

Project Title: The Interaction Between Apelin and the Renin-Angiotensin-Aldosterone System

Project Summary: Hypertension is broadly defined as increased blood pressure, and is accompanied by structural changes in the heart, blood vessels, and the kidney. The clinical manifestations include left-ventricular hypertrophy (an enlarged heart), arterial remodeling (stiff arteries), and nephrosclerosis (scarring of the kidney tissue). The renin-angiotensin-aldosterone system (RAAS) plays an integral role in maintaining blood pressure by constricting blood vessels and balancing fluid and salt in the body. Inhibition of this system by drugs such as Privilin (lisonopril) and Atacand (candesartan) has found widespread use for the treatment of hypertension. Independent of its effects on blood pressure, the RAAS has been implicated in the structural changes in vascular tissues often associated with hypertension. Smoking is a key risk factor for heart disease and hypertension in particular, and leads to structural changes in the blood vessels. How this vascular remodeling occurs is not understood. Smoking activates the RAAS, which may explain in part the effects of smoking on the structure of blood vessels.

Apelin is a newly discovered protein that acts on blood vessels to cause relaxation and thus lower blood pressure. Recent studies into how apelin works revealed that apelin could counteract the effects of the RAAS. These observations led us to propose the hypothesis that apelin interacts with the RAAS to balance the effects of that system on both blood pressure and vascular structural remodeling. The long-term goal of this study is to establish apelin as a counter-regulator of the RAAS and as a potential target for new drugs for the treatment of hypertension.

To address this hypothesis we propose three specific aims:

Specific Aim 1: To test the hypothesis that apelin modulates the development of vascular fibrosis in response to angiotensin II. In this aim, experiments will utilize mouse models of hypertension to determine the effects of apelin on blood pressure, cardiac function, and vascular fibrosis.

Specific Aim 2: To characterize the mechanistic interaction between apelin and the RAAS in hypertension. Aim 2 will include a detailed characterization of the effects of RAAS blockade, and thiazide diuretics on apelin in vivo.

Specific Aim 3: To test the hypothesis that the apelin receptor directly modulates the function of the angiotensin II receptor. Experiments include proteomic analysis of receptor complexes from cells and tissues, and a cell-based high-throughput screen to identify the protein-protein interaction domains between the apelin and AT1 receptor.

We anticipate that these studies will establish a clear mechanistic links between the RAAS and the apelinergic system. Results from this study may provide new mechanistic

As of July 1, 2006

James & Esther King Biomedical Research Program

insights into the molecular pathology of smoking related arterial stiffness and hypertension.