

Arendshorst Lab: ROTATION PROJECTS – 2010 - 2011

The molecular basis of hypertension is complex, involving multiple genes and environmental factors that interact in an overlapping mosaic pattern. The kidneys play a central role in regulating arterial pressure (AP), and severe renal disease is accompanied by hypertension. Common renal abnormalities during the development of hypertension are exaggerated renal vascular reactivity to vasoconstrictor agents, oxidative stress and endothelial dysfunction with attenuated responses to vasodilator factors, causing or acting in concert with abnormal renal retention of salt and water.

The Arendshorst laboratory of Renal Physiology and Vascular Biology in the Department of Cell and Molecular Physiology studies the function of preglomerular afferent arterioles and their vascular smooth muscle cells that are primary regulators of blood flow and glomerular filtration in the kidney. Renal blood flow studies assess renal vascular reactivity in anesthetized rats and mice. Fluorescent imaging (fura-2) studies elucidate cellular mechanisms of Ca^{2+} entry and mobilization in isolated arterioles or smooth muscle cells. More comprehensive descriptions of the laboratory, investigators and research interests are provided at <http://www.med.unc.edu/physiology/facarendshorst.htm>. Our research is funded by the NIH.

Our current research interests focus on cellular Ca^{2+} signal transduction pathways mediating the actions of G-protein coupled receptor (GPCR) agonists. We find that GPCR agonists stimulate superoxide anion ($\bullet O_2^-$) production that activates a relatively underappreciated second messenger system involving ADP ribosyl (ADPR) cyclase, ryanodine receptors (RyR), and Ca^{2+} -induced Ca^{2+} release (CICR) from sarcoplasmic reticulum of renal vascular smooth muscle cells (Fig. 1). This enzymatic pathway centers on ADPR cyclase production of two adenine dinucleotides, cADPR and NAADP, both of which are significant regulators of Ca^{2+} release from different internal stores (Fig. 1). Before we started our studies, very little was known about this pathway and its pivotal role in Ca^{2+} mobilization in the renal microcirculation. Our recent findings highlight the importance of this system in transducing GPCR signals to $[Ca^{2+}]_i$ responses in afferent arterioles *in vitro* and renal vasoconstriction *in vivo*.

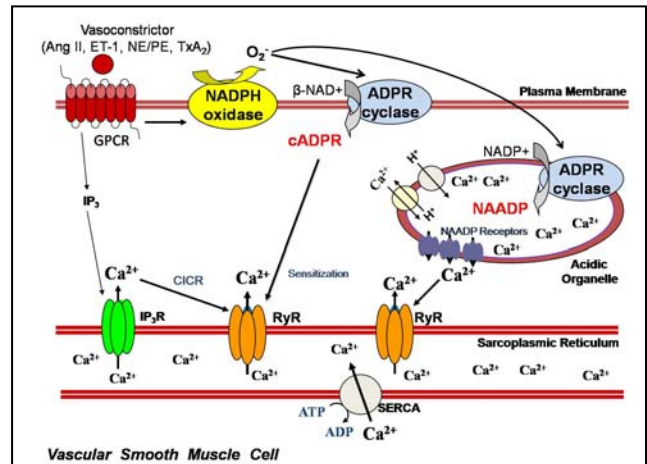
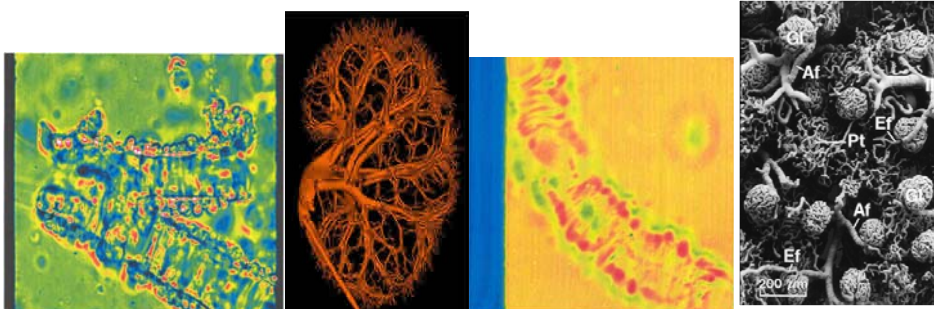


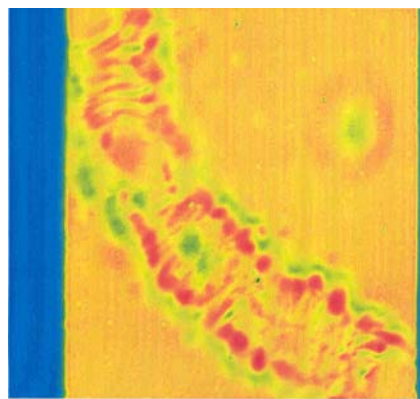
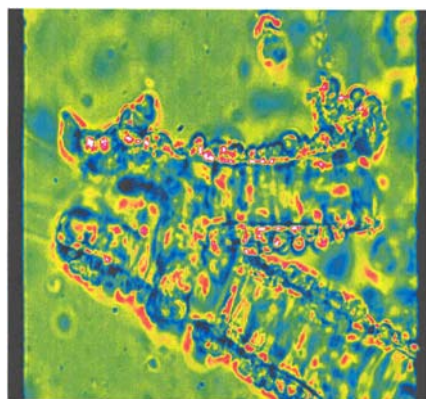
Fig. 1. Working model of ADPR cyclase-mediated- Ca^{2+} signaling in afferent arteriolar VSMC. For the sake of simplicity, Ca^{2+} entry channels (L-type, store-operated, receptor operated) and other ion channels (e.g., K and Cl) have been omitted. "ADPR cyclase" represents the novel renal ADPR cyclase and conventional CD38.

See Dept of Cell & Molecular Physiology Faculty Web Page for examples of Rotation Projects for Fall Semester 2009.



Listed below are several examples of topics for Rotation Projects for Fall Semester 2010 or Spring Semester 2011. A general goal for the student is to have a meaningful research experience with an understanding of the scientific method as used in the conduct of lab projects. A rotation slot is open for the 2010 – 2011 academic year.

- Evaluate the importance a novel renal specific ADPR cyclase and its cyclic ADP ribose / ryanodine receptor Ca^{2+} signaling pathway in renal vascular reactivity in vivo. Student will perform surgery on an anesthetized rat or mouse and measure renal blood flow using an ultrasonic transducer. Renal vascular reactivity is assessed in response to vasoactive agents injected iv or directly into the renal artery to produce transient renal vasoconstriction.
- Determine the functional importance of a novel renal specific ADPR cyclase and cyclic ADP ribose / ryanodine receptor Ca^{2+} signaling pathway in vascular smooth muscle cells of afferent arterioles. Student will isolate preglomerular resistance arterioles (<100 μ m in diameter) using an iron oxide/sieving method or microdissection and measure cytosolic Ca^{2+} concentration utilizing the fluorophore fura-2 in imaging studies. Arterioles are isolated from mice lacking the conventional ADPR cyclase, CD38, due to gene targeting.
- Assess the relative activities of a novel renal ADP ribosyl cyclase vs. conventional CD38. Student will use a biochemical assay to measure production of the metabolite cyclic ADP ribose in afferent arterioles isolated from CD38^{-/-} and wild-type mice.
- Identify specific ryanodine receptor subtypes (RyR1-3) in vascular smooth muscle cells of afferent arterioles. Student will utilize real-time RT-PCR to quantify mRNA of each subtype.



Suggested background reading includes chapters on kidney function and regulation of renal hemodynamics and glomerular filtration rate in a medical student textbook of physiology such as one edited by Boron and Boulpaep or Guyton and Hall. A general understanding of original research articles as well as review papers published by Dr. Arendshorst and associates would be helpful. The laboratory meets weekly for an informal journal club discussion of current literature and review progress of recent results of ongoing research projects.