

BIOGRAPHICAL SKETCH

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NAME Arendshorst, William J.	POSITION TITLE Professor		
eRA COMMONS USER NAME Arendshorst			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
DePauw University, Greencastle, IN	BA	1966	Biological Sciences
Indiana University, Medical Center, Indianapolis, IN	PhD	1970	Physiology

A. Personal Statement: I believe I am qualified and well suited to be an investigator on the proposed studies as I have conducted research on renal hemodynamics and control of sodium excretion throughout my academic career. In addition to assessing whole kidney blood flow using clearance methodology, I have investigated glomerular dynamics and nephron salt transport at the single nephron level using micropuncture methods. I was the first to measure renal blood flow in a rat kidney using an electromagnetic transducer and more recently an ultrasonic transit-time flow meter. I have measured superficial cortical regional blood flow using a fiberoptic-laser Doppler system. I have had considerable experience using the ultrasonic transit-time methodology to measure renal blood flow in a mouse kidney. We have recently characterized dynamic responses of renal vascular resistance to characterize intrarenal mechanisms with different time constants to determine their relative contributions to overall autoregulation of renal blood flow to a rapid, single-step increase in renal perfusion pressure.

My laboratory has had extensive experience studying renal vascular reactivity and mechanisms regulating sodium excretion in rats and more recently mice. Directly relevant to the proposed studies, we have investigated renal vasoconstriction in vivo produced by angiotensin II and phenylephrine as well as perfusion pressure and modulation by nitric oxide and reactive oxygen species. We have also published on renal vasodilation produced by acetylcholine and bradykinin and mediation by nitric oxide and prostanoids. We have extensive experience in calcium signaling pathways in isolated afferent arterioles and their vascular smooth muscle, with particular recent interest in the CD38 ADP ribosyl cyclase and calcium-induced calcium release mediated by ryanodine receptors.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1970 - 1971. NIH Postdoctoral Fellow, Dept. of Physiology, Indiana Univ Medical Center (E.E. Selkurt).
1971 - 1974. NIH Postdoctoral Fellow, Depts. of Medicine & Physiology, UNC-CH (C.W. Gottschalk).
1974 - 2012. Department of Cell & Molecular Physiol, UNC-CH. Part-time Lecturer (1971- 74), Assist. Prof. (1974-79), Assoc. Prof. (1979-86), Professor (1987-2012), Interim Chair (2000-2002).
2000-pres. McAllister Heart Institute (Carolina Cardiovascular Biology Center), UNC-CH, Member.
2005-pres. UNC Kidney Center, UNC-CH, Member and Internal Advisory Committee
2012 – pres. Department of Cell Biology and Physiology, UNC-CH. Professor (2012 – present).

Awards / Honors / Service

NIH Research Career Development Award, 1980-1985.
American Journal of Physiology: Renal Physiol. Editorial Board, 1985-89; Assoc. Editor, 1989-1994.
American Journal of Physiology: Regul Integrative Comparative Physiol. Editorial Board, 1994-2007.
American Journal of Hypertension, Editorial Board, 2000-2010.

Hypertension, Editorial Board, 1995 - present.

Amer Heart Association, NC Affiliate, Research Review Committee, (Member: 1980-1983, 1993-1996).

Amer Physiol Society: Section Advis Comm (1987-89). Renal Section: Secry, 1985-87; Chair, 1987-90.

American Heart Association, Cardiorenal Research Study Committee (Member: 1988-1990).

NIH, Cardiovascular-Renal Study Sec, Ad hoc (1983, 1988, 1992-93; 1996, 1998-99); Member (1993-96).

NIH, Hypertension and Microcirculation Study Section, Ad hoc, 2009, 2010.

NIH, Review/Site Visit Team, Heart, Blood & Lung Institute (1985, 1987, 1991-1993; 1997, 2006, 2008, 2009, 2010).

NIH, NIDDK-Special Grants Review Comm (Subcomm D). Member, 1999-2003. Ad hoc (2003).

FASEB Summer Conf on Renal Hemodynamics, Organizing Comm, 1988-1989, 1999-2007. Chair 2007.

American Heart Association, Council-High Blood Pressure Research, Program Comm (2001-2003; 2007 – present) & Awards Comm (2006-2009).

Carl W. Gottschalk Award and Lectureship, American Physiological Society, April 2003.

Visiting Professor, Center for Hypertension and Metabolic Diseases, University, Chongqing, China, November 2008.

C. Selected Peer-Reviewed Publications (in chronological order). (selected from ~ 110)

- Facimire, CS, PJ Mohler and **WJ Arendshorst**. Expression and relative abundance of short transient receptor potential channels in rat renal microcirculation. *Am J Physiol-Renal Physiol* 286: F546-F551, 2004. PMCID: 14678949
- Just A, AJM Olson and WJ Arendshorst. Dual constrictor and dilator actions of ET_B receptors in the rat renal microcirculation: Interactions with ETA receptors. *Am J Physiol-Renal Physiol* 286: F660-F668, 2004. PMCID: 14678950
- Just, A, AJM Olson, JR Falck, **WJ Arendshorst**. Nitric oxide and NO-independent mechanisms mediate ET_B receptor buffering of ET-1-induced renal vasoconstriction in the rat. *Am J Physiol Regul Integr Comp Physiol* 288: R1168-R1177, 2005. PMCID: 15618347
- Fellner, SK and **WJ Arendshorst**. Angiotensin II, reactive oxygen species and Ca²⁺ signaling in afferent arterioles. *Am J Physiol Renal Physiol* 289: F1012-F1019, 2005. PMCID: 15942049
- Just, A and **WJ Arendshorst**. Nitric oxide blunts myogenic autoregulation in rat renal but not skeletal muscle circulation via tubuloglomerular feedback. *J Physiology (London)* 569: 959-974, 2005. PMCID: 16223765
- Just A, AJ Olson, CL Whitten and **WJ Arendshorst**. Superoxide mediates acute renal vasoconstriction produced by angiotensin II and catecholamines by a mechanism independent of nitric oxide. *Am J Physiol Heart Circ Physiol* 292: H83-H92, 2007. PMCID: 16951043
- Thai T, SK Fellner and **WJ Arendshorst**. ADP-ribosyl cyclase and ryanodine receptor activity contribute to basal renal vasomotor tone and agonist-induced renal vasoconstriction in vivo. *Am J Physiol - Renal Physiol* 293: F1107-F1114, 2007. PMCID: 17652368
- **Arendshorst, WJ** and LG Navar. Renal Circulation and Glomerular Hemodynamics. Chapter 2, Volume 1. Eighth Edition of *Diseases of the Kidney*, edited by R.W. Schrier, Lipincott Williams and Wilkins. 2007, pp. 54-95.
- Just, A, CL Whitten and **WJ Arendshorst**. Reactive oxygen species participate in acute renal vasoconstrictor responses induced by ET_A- and ET_B-receptors. *Am J Physiol Renal Physiol* 294: F719-F728, 2008. PMCID: 18256310
- Thai, TL and **WJ Arendshorst**. ADP-ribosyl cyclase and ryanodine receptors mediate endothelin ET_A and ET_B receptor-induced renal vasoconstriction in vivo. *Am J Physiol Renal Physiol*. 64: F360-F368, 2008. PMCID: 18524860
- Navar, LG, **WJ Arendshorst**, TL Pallone, EW Inscho, JD Imig, and PD Bell. The Renal Microcirculation. *APS Handbook of Physiology, Microcirculation*, 2nd edition, 2008, RF Tuma, WN Duran, and K Ley, Editors, Boston, Academic Press (Elsevier), pp 550-683.
- **Arendshorst, WJ** and TL Thai. Regulation of the renal microcirculation by ryanodine receptors and calcium-induced calcium release. *Curr Opin Nephrol Hypertens* 18: 40-49, 2009. PMCID: 19077688
- Thai, TL and **WJ Arendshorst**. Mice lacking the ADP ribosyl cyclase CD38 exhibit attenuated renal vascular reactivity to angiotensin II, endothelin-1 and norepinephrine. *Am J Physiol-Renal Physiol* 297: F169-F176, 2009. PMCID: PMC-2711707.
- Just, A, L Kurtz, C de Wit, C Wagner, A Kurtz, and **WJ Arendshorst**. Connexin 40 mediates the

tubuloglomerular feedback contribution to renal blood flow autoregulation. *J Amer Soc Nephrol* 20: 1577-1585, 2009. PMID: PMC-2709687.

- Fellner, SK and **WJ Arendshorst**. Complex interactions of NO/cGMP/PKG systems on Ca²⁺ signaling in afferent arteriolar vascular smooth muscle. *Am J Physiol-Heart Circ Physiol* 298: H144-H151, 2010.
- **Arendshorst, WJ** and LG Navar. Renal Circulation and Glomerular Hemodynamics. Chapter 3 Volume 1. Ninth Edition of *Diseases of the Kidney and Urinary Tract*, edited by R.W. Schrier, E. Nielson, T. Coffman and R. Falk. Lipincott Williams and Wilkins. 2012, In Press.
- **Arendshorst, WJ**. Editorial Focus. Connexin 40 mediates tubuloglomerular feedback paracrine signaling by coupling tubular and vascular cells in the renal juxtaglomerular apparatus. *Am J Physiology Renal Physiol* 303:Fx-Fx, 2012. (In Press).

C. Ongoing Research Support

- NIH RO1 HL-02334-54. "Renal Vascular Reactivity in Hypertension"
PI: W.J. Arendshorst. 12/15/2010 – 12/14/2014.

CD38 ADP ribosyl (ADPR) cyclase is a membrane-bound enzyme that produces metabolites known to promote Ca²⁺ mobilization mediated by ryanodine receptors (RyR) in arteriolar smooth muscle cells. We postulate that renal CD38 is central to the development of angiotensin II-induced hypertension and that CD38-deficient mice exhibit less pronounced renal vasoconstriction, Na⁺ retention and hypertension than do wild-type (WT) mice infused with Ang II. The goals are to test the hypotheses that: 1) CD38 ADPR cyclase participates in the development of Ang II-induced hypertension such that Ang II produces less pronounced hypertension in CD38^{-/-} (global genetic deficiency) vs. WT mice, with less severe hypertension predicted in WT mice with targeted, renal-specific partial knockdown of CD38 induced by siRNA; 2) CD38 ADPR cyclase contributes to renal vasoconstriction and the rightward shift in the pressure-natriuresis relation in Ang II-induced hypertension; and 3) CD38 is the major ADPR cyclase mediating G-protein coupled receptor-elicited Ca²⁺ signaling involving RyR Ca²⁺-induced Ca²⁺ release in isolated afferent arterioles and renal vasoconstriction *in vivo*.

- NC TraCS Award # 550KR41224. "A Novel Regulator of Renal Sodium Excretion"
Co-PIs: R Tarran and WJ Arendshorst. 1/2013-1/2015.

Renal Na⁺ excretion is fine tuned along the distal tubule and collecting duct by the epithelial Na⁺ channel (ENaC). Short palate, lung and nasal epithelial clone 1 (SPLUNC1) is an epithelial peptide expressed and secreted by the lung airway. We will test the hypothesis that SPLUNC1 is an important regulator of Na⁺ excretion by the kidney and thus electrolyte homeostasis by challenging wild type vs. SPLUNC1 knockout mice with different Na⁺ loads to determine how rapidly they excrete the acute loads. A better understanding of renal SPLUNC1 interactions may lead to the development of novel therapeutics to treat hypertension.

Completed Research (in last 3 years)

- NIH RO1 HL-02334-54. "Renal Vascular Reactivity in Genetic Hypertension"
PI: W.J. Arendshorst. 7/1/2006 – 12/14/2010.

The central goals are to evaluate the *in vivo* renal vascular responsiveness to GPCR agonists (Ang II, ET-1, and prostanoids) and to assess intracellular Ca²⁺ signaling pathways in VSMC of isolated preglomerular microvessels of normotensive and genetically hypertensive SHR rats. Specific aims were: 1) to assess cellular Ca²⁺ signals mediating actions of GPCR vasoactive agents *in vitro* and *in vivo*, 2) to evaluate vascular reactivity *in vivo* to explain exaggerated renal vasoconstriction in young SHR, 3) to investigate regulation of GPCR in preglomerular resistance arterioles, and 4) to define the contribution of reactive oxygen species (ROS) and kinase pathways to VSMC Ca²⁺ signaling and renal vascular responsiveness.

- NIH RO1 HL-078980-5. "Intestinal peptides in volume homeostasis."
PI: Michael Goy, Ph.D. 7/1/05 – 6/30/2010. Role: Investigator

Principal Investigator/Program Director (Last, First, Middle):