

BIOGRAPHICAL SKETCH

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NAME Arendshorst, William J.		POSITION TITLE	
eRA COMMONS USER NAME (credential, e.g., agency login) Arendshorst		Professor	
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)
DePauw University, Greencastle, IN		BA	1966
Indiana University, Medical Center, Indianapolis, IN		PhD	1970
			Biological Sciences
			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 throughout my academic career. In addition to assessing whole kidney blood flow using clearance methodology, I have investigated glomerular dynamics 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.

I am highly qualified to be PD/PI of the proposed studies in our competitive renewal entitled "Renal Vascular Reactivity in Hypertension." I was an active investigator on Carl W Gottschalk's grant from 1974-1992 and assumed leadership role of this RO1 as PD/PI for the past 18 years. I have the experience, expertise, leadership and motivation required to successfully conduct the proposed research. I have a demonstrated record of meritorious, productive original investigation in areas highly relevant to renal dysfunction and the pathogenesis of hypertension. Our productive research team has pioneered insightful studies of Ca²⁺ signaling in the renal microvasculature and of regulation of vascular reactivity in kidneys during health and genetic hypertension. Recent contributions have demonstrated the significant functional role of reactive oxygen species and adenine dinucleotides in Ca²⁺ signal transduction and vasomotor tone in healthy kidneys. We propose to extend such studies to the important role of the ADP ribosyl cyclase and ryanodine-mediated Ca²⁺-induced Ca²⁺-release in the renal vasculature in the pathogenesis of hypertension induced by chronic infusion of angiotensin II.

B. Positions and Honors

Positions

- 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 - pres. Department of Cell & Molecular Physiol, UNC-CH. Part-time Lecturer (1971- 74), Assist. Prof.(1974-79), Assoc. Prof. (1979-86), Professor (1987-pres.), 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

Awards / Honors / Service

- NIH Research Career Development Award, 1980-1985.
- American Journal of Physiology: Renal Physiol. Editorial Board, 1985-89; Assoc. Editor, 1989-94.
- American Journal of Physiology: Regul Integrative Comparative Physiol. Editorial Board, 1994-2007.
- American Journal of Hypertension, Editorial Board, 2000-present.
- 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/Program Projects, Heart, Blood & Lung Institute (1985, 1987, 1991-1993;
 1997, 2006, 2008 - 2011).
 NIH, NIDDK-Special Grants Review Comm (Subcomm D). Member, 1999-2003.Ad hoc (2003).
 FASEB Summer Conf on Renal Hemodynamics, Organize 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 Lectureship, American Physiological Society, April 2003.
 Visiting Professor, Third Military University, Chongqing, China, November 2008.

C. Peer-Reviewed Publications (selected from ~ 115)

Most Relevant to Current Application:

- 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. PMID-14678950.
- Fellner, SK and **WJ Arendshorst**. Angiotensin II Ca²⁺ signaling in rat afferent arterioles: stimulation of cyclic ADP ribose and IP₃ pathways. *Am J Physiol- Renal Physiol* 288: F785-F791, 2005. PMID: 15598842.
- 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. PMID: 15942049.
- 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. PMID- 16951043.
- Fellner, SK and **WJ Arendshorst**. Voltage-gated Ca²⁺ entry and ryanodine receptor Ca²⁺-induced Ca²⁺ release in preglomerular arterioles. *Am J Physiol Renal Physiol* 292: F1568-F1572, 2007. PMID-1719096.
- Vågnes, OB, BM Iversen and WJ Arendshorst. Short-term Ang II produces renal vasoconstriction independent of TP receptor activation and TxA₂ / isoprostane production. *Am J Physiol-Renal Physiol* 293: F860-F867, 2007. PMID-17567934.
- 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. PMID-17652368.
- 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: F719-728, 2008. PMID-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: PMC-2419186.
- **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. PMID-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.
- Thai, TL, GC Churchill, and **WJ Arendshorst**. NAADP receptors mediate calcium signaling stimulated by endothelin-1 and norepinephrine in renal afferent arterioles. *Am J Physiol-Renal Physiol* 297: F510-F516, 2009. PMCID: PMC-2724244.
- Moss, NG, DA Rigeura, RM Solinga, MM Kessler, DP Zimmer, **WJ Arendshorst**, MG Currie and MF Goy. The natriuretic peptide uroguanylin elicits physiologic actions through distinct topoisomers. *Hypertension* 53: 867-876, 2009. PMCID: 19289652

- 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. PMID: 2806127
- Kogan K, K Johnson, S Feingold, N Garrett, IM Guracar, **WJ Arendshorst** and PA Dayton. Validation of dynamic contrast-enhanced ultrasound in rodent kidneys as an absolute quantitative method for measuring blood perfusion. *Ultrasound Med Biol* 37: 900-908, 2011. Pub Med - In Process.

Recent Publications of Importance to the Field

- **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.
- 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.

D. Ongoing Research Support

- NIH RO1 HL-02334-54. “Renal Vascular Reactivity in Hypertension”
PI: W.J. Arendshorst. 12/15/2010 – 11/30/2014.

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*.

Completed Research (in last 3 years)

- NIH RO1 HL-02334-54. “Renal Vascular Reactivity in Genetic Hypertension”
PI: W.J. Arendshorst. 7/1/2006 – 6/30/2011 (one year no-cost extension).

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

Aims are: 1) to characterize intestinal release of proUGn into plasma and its excretion in urine in response to acute and chronic NaCl loads in conscious rats and to test the hypothesis that intestinal, plasma and urinary pro-UGn levels vary as a function of oral salt intake, 2) to evaluate the effects of proUGn on renal function in anesthetized rats and gain insight into the efficacy and mechanism of pro-UGn's actions on the kidney, and 3) to determine the structural identity active principal responsible for natriuretic actions of proUGn.