Research Experience in Hypertension, Cardiovascular and Renal Pathobiology

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Project Description

Current research programs in Dr. Navar's laboratory are related to the regulation of renal hemodynamics and glomerular filtration rate (GFR) by paracrine factors, the hormonal control of sodium excretion and renal hemodynamics, the interrelationships between renal hemodynamics and sodium excretion and the pathophysiology of angiotensin II (Ang II) dependent hypertension. One important intrarenal mechanism for GFR regulation is the "macula densa feedback mechanism". By this mechanism, changes in composition of the fluid within the lumen of the distal tubule are sensed and signals are then sent to vascular contractile cells which regulate GFR and renal blood flow. This mechanism has been studied extensively to determine the luminal component which is responsible for initiating feedback responses and how the macula densa cells transmit signals. Recent studies have evaluated the potential role of ATP in mediating feedback signals. Another area of emphasis regards the intrarenal actions of angiotensin II. While earlier studies had emphasized the role of angiotensin II in the control of blood flow and GFR, more recent studies have focused on the importance of angiotensin in regulating tubular sodium reabsorption rate. Ang II exerts synergistic effects to alter proximal reabsorption and enhance the sensitivity of the macula densa feedback mechanism in order to allow Ang II to exert a sustained influence on distal tubule volume delivery and sodium excretion.

Another area of emphasis is the evaluation of the intrarenal mechanisms responsible for mediating changes in sodium excretion that occur in response to changes in arterial pressure. This phenomenon is termed "pressure natriuresis." We have determined the relative contributions of the renin-angiotensin system, the intrarenal prostaglandin system and nitric oxide in mediating this response. Several recent studies have provided evidence supporting a major role for nitric oxide in mediating arterial pressure related changes in sodium excretion.

Studies related to the pathophysiology of hypertension have addressed kidney function in the two-kidney, one-clip hypertensive rat model and in angiotensin dependent hypertension. One of the most interesting aspects of this model is that the non-clipped kidney seems to be under substantial influence of Ang II which is generated as a consequence of the clip on the opposite kidney. Using a model of Ang II dependent hypertension, the role of altered renal internalization and formation of Ang II in mediating changes in renal function is being evaluated. In addition, the mechanism responsible for maintaining high intratubular concentrations of Ang II is being investigated. We have also shown that Ang II is formed within the kidney and is increased in Ang II dependent hypertension. Ang II stimulates the expression and synthesis of angiotensinogen which contributes to the high levels of Ang II in the kidney and the development and maintenance of hypertension.