The Intrarenal Renin-Angiotensin-System in Pathophysiology of Hypertension

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The intrarenal renin angiotensin system (RAS) regulates the renal vasculature and tubular transport function during variations in salt intake. When inappropriately increased; however, the intrarenal RAS causes renal vasoconstriction, sodium retention, impaired pressure natriuresis and progressive development of hypertension. These effects are mediated by augmented levels of angiotensin (Ang) II that are greater than occurs systemically. Intrarenal Ang II content is increased by angiotensin type 1 (AT1) receptor mediated uptake of circulating Ang II as well as de novo intrarenal Ang II generation as a consequence of augmentation of intrarenal angiotensinogen (AGT) mRNA and protein in proximal tubule cells. The AGT is secreted into the tubular lumen leading to Ang I and Ang II formation thereby stimulating proximal sodium reabsorption rate. The AGT secreted into the proximal tubule also spills over into distal nephron segments providing substrate for further downstream Ang I and Ang II generation. The expression of renin mRNA and protein in principal cells of collecting ducts are also augmented in Ang II dependent hypertension, and combined with the persisting activity of angiotensin converting enzyme (ACE), contribute to increased distal nephron Ang II levels and stimulation of distal nephron sodium reabsorption. In the presence of ACE inhibition, chronic Ang II infusions fail to upregulate intrarenal Ang II levels and do not cause progressive hypertension. Thus, in Ang II-dependent hypertension, renin and ACE in distal nephron segments provide a critical final mechanism for Ang II formation and consequently play a major role in the development and maintenance of high blood pressure.