Kidney angiotensinogen as a cardinal risk factor in hypertension

High blood pressure is prevalent in over 30% of the adult population and accounts for approximately one fourth of patients with heart failure, especially the elderly. The renin-angiotensin system (RAS) is of critical importance in the regulation of blood pressure and body fluid volumes. The RAS forms several angiotensin molecules which act on blood vessels and organs to protect us from excess loss of salt. Angiotensin II (Ang II) is the most powerful and inappropriate activation of RAS contributes to the development of high blood pressure and associated organ damage including injury to the kidneys. Angiotensinogen (AGT) protein is the source of Ang II, and is produced mainly in the liver but also in the kidneys. Accordingly, the regulation of AGT is a key mechanism facilitating the progression of high blood pressure. Indeed it has been shown that blood pressure is increased in genetically modified animal models that overproduce AGT.

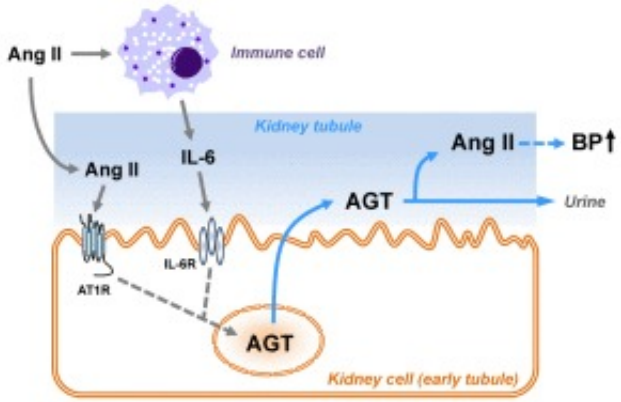

Fig. 1. Mechanisms underlying Ang II amplification by upregulation of kidney AGT
Ang II: Angiotensin II, IL-6: Interleukin 6, AT1R: Ang II type 1 receptor, IL-6R: IL-6 receptor, AGT: Angiotensinogen, BP: Blood pressure

Our studies have demonstrated that AGT and Ang II are produced in cells located in the first part of the kidney tubules that form urine known as nephrons. Increased AGT in these tubules will produce more Ang II within the tubular fluid. When experimental animals receive Ang II infusions, there is activation of the kidney RAS including increased kidney AGT leading to more Ang II formed in the kidneys and elevated blood pressure. Blockade of prominent type 1 Ang II receptors prevents the increases in kidney AGT and in blood pressure. Thus, elevated Ang II stimulates kidney AGT production which then leads to its secretion into the urine and more Ang II production which further accelerates the development of high blood pressure and injury to the kidneys and other tissues.

We have proposed that urinary AGT levels provide an index of kidney RAS activation in

hypertension. The elevated urinary AGT levels have also been demonstrated in non-hypertensive diseases. Animal models and patients with diabetic mellitus also exhibit greater urinary AGT levels. Importantly, urinary AGT augmentation occurs before there is protein in the urine which is a marker of kidney injury. These findings suggest that elevated urinary AGT may predict the development of kidney injury in patients with high blood pressure and diabetes. Elevated urinary AGT levels also occur in patients with chronic kidney diseases, conditions which are associated with an increased state of inflammation.

Our recent studies have revealed that interleukin 6 (IL-6), which is a factor inflaming organs and induced by Ang II, is required for the Ang II-induced AGT elevation in the kidney cells. Since IL-6 is robustly produced by an activated immune system in high blood pressure, immune system activation and IL-6 production also contribute to the stimulation of kidney AGT. Studies have shown that immunosuppressive treatment and gene deletion of IL-6 prevent the Ang II-induced elevation of blood pressure.

In conclusion, in Ang II-induced hypertension, and other conditions such as diabetes, there is a progressive stimulation of kidney AGT production, which depends on synergistic effects of Ang II receptor activation with an activated immune system and increased IL-6. The elevation of kidney AGT production increases the amount of AGT secreted into the renal tubular fluid leading to additional intratubular Ang II formation. These increases then stimulate salt reabsorption by transport systems in the nephrons leading to more fluid retention. In addition to stimulating transport, the combined increases in kidney Ang II and stimulation of inflammatory factors lead to progressive tissue injury and sustained high blood pressure. Moreover, the findings provide evidence that urinary AGT can be clinically useful as a predictor of kidney injury in hypertension and diabetes, and to assess the efficiency of drug treatments.

Ryousuke Satou and L. Gabriel Navar
Department of Physiology and the Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, LA, USA

Publication

Role of stimulated intrarenal angiotensinogen in hypertension.
Satou R, Shao W, Navar LG
Ther Adv Cardiovasc Dis. 2015 Aug