Regulation of blood pressure by renal proximal tubule transport

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The Na^+/HCO_3^- cotransporter (NBCe1) in the basolateral side of the renal proximal tubule (PT) plays a pivotal role in the regulation of systemic acid/base balance. Mutation of NBCe1 causes severe proximal renal tubular acidosis (RTA) accompanied by ocular and other extrarenal disorders. Importantly, PT acid/base transport is coupled with Na^+ transport.

The PT reabsorbs approximately 70% of Na^+ filtered in the glomerulus, thereby contributing to the regulation of plasma volume and blood pressure. Besides NBCe1, there are other Na^+ transporters in the PT, such as Na^+/H^+ exchanger 3 (NHE3) on the apical side and Na^+,K^+-ATPase (NKA) on the basolateral side. These Na^+ transporters are regulated by hormones such as angiotensin II (AngII) and insulin.

In particular, AngII is thought to be the most important stimulator of Na^+ reabsorption, and studies have shown that NBCe1, NHE3, and NKA, are also stimulated via AngII receptor. Specific deletion of AT_{1A}, the most important AngII receptor, in the PT alone has been shown to be sufficient to lower blood pressure, indicating that AT_{1A} in the PT is crucial for the elevation of systemic blood pressure by AngII. Intriguingly, in rodents and rabbits, the effect of AngII on PT NBCe1 is biphasic. At low concentration (10^{-10}M), AngII stimulates NBCe1 via PKC/cAMP/ERK, while at high concentration (10^{-6}M), AngII inhibits NBCe1 via NO/cGMP/cGKII. In contrast, in human PT, we have found that AngII has a dose-dependent monophasic stimulatory effect on NBCe1 mediated by NO/cGMP/ERK. These differences seem to be due to the species differences of the AngII signal transduction system.

Insulin, another important modulator of PT transport, has multipotent effects on several organs and tissues. Insulin signaling is principally mediated via the insulin receptor substrate (IRS)-PI3K-Akt signaling cascade, which is responsible for its multipotent effects. Among several IRS subtypes, IRS1 and IRS2 play the main roles in mediating the insulin signaling. In the PT, the stimulatory effect of insulin on Na^+ reabsorption is IRS2-dependent which can be inhibited by wortmannin. We found that even in the PTs of insulin resistant animals and humans, this IRS2-dependent stimulatory effect of insulin on NBCe1 was preserved, although IRS1-mediated glucose uptake in adipocytes was severely reduced. Further, this stimulatory effect was still preserved even in animals with type 2 diabetes (T2DM) and overt nephropathy. Our results demonstrate that the stimulation of Na^+ reabsorption by insulin in the PT is mediated by the insulin/IRS2/PI3K pathway. As hyperinsulinemia is frequently seen in insulin resistance and T2DM, our results suggest that the preserved stimulation of the insulin/IRS2/PI3K pathway in the PT could lead to enhanced Na^+ reabsorption, thereby contributing to the emergence and progression of hypertension associated with

metabolic syndrome.

In this invited lecture we will present recent findings regarding the role of PT transport on regulating blood pressure, focusing on the effects of AngII and insulin.