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Oral presentation

Role of cGMP in natriuresis and pressure-natriuresis

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Cyclic GMP (cGMP) is synthesized by renal proximal tubule (RPT) cells and is exported from these cells into the renal interstitial (RI) compartment by an organic anion transporter system. We have demonstrated that RI gGMP inhibits renal Na^+ reabsorption at the renal tubule. We have further demonstrated that cGMP-induced natriuresis can be blocked by intrarenal pharmacological inhibition of protein kinase G (PKG). In order to demonstrate that RI cGMP is a potent physiological regulator of Na^+ excretion, we selectively decreased RI cGMP using an RI infusion of cGMP-specific phosphodiesterase (PDE), which does not cross the cell membrane and is confined to the extracellular space because of its molecular size. cGMP PDE selectively decreased extracellular RI cGMP levels, without influencing cAMP levels, and caused significant antinatriuresis. On the other hand, blockade of cGMP degradation with selective cGMP PDE inhibitor, zaprinast, increased both RI cGMP and sodium excretion, independently of systemic or renal hemodynamic changes. Therefore, extracellular RI cGMP plays an important role in the regulation of renal Na^+ excretion.

Pressure-natriuresis (P-N) is the major regulatory mechanism in mammalian physiology whereby an elevation in blood pressure (BP) induces a rapid increase in renal Na^+ excretion. P-N normally protects the organism from a long-term rise in BP by reducing extracellular fluid volume. Virtually all forms of hypertension in experimental animals and humans are accompanied by a defective natriuretic response to increased BP. Thus, in the hypertensive state a normal rate of Na^+ excretion is achieved only at the expense of increased BP. In an experimental rat P-N model, we demonstrated that increasing renal perfusion pressure (RPP) rapidly releases cGMP into the RI space. The RPP-induced increase in RI cGMP was accompanied by natriuresis due to inhibition of RPT Na^+ reabsorption as indicated by increased in fractional Na^+ and Li^+ excretion and no change in glomerular filtration rate (GFR). When cGMP export from the tubule cell was blocked by administration of organic anion transport inhibitor probenecid, the pressure-induced icrements in both RI cGMP and Na^+ excretion were eliminated. P-N as well as the increase in RI cGMP were also blocked by intrarenal inhibition of cGMP formation using guanylyl cyclase inhibitor ODQ (1-H-[1,2,4]oxadiazolo[4,2-α]quinoxalin-1-one). P-N also was blocked by intrarenal administration of PKG inhibitor Rp-8-pCTP-cGMPs. These results strongly suggest that P-N is mediated by RI cGMP.

Studies in human RPT cells confirmed the antinatriuretic action of cGMP *in vivo*. We employed the Na^+-sensitive indicator Na-Green to measure changes in intracellular Na^+ in response to NO donor SNAP (S-nitroso-N-acetylpenicillamine), cGMP and 8-Br-cGMP. RPT cells were studied in the presence of ouabain, an inhibitor of Na^+/K^+ ATPase. SNAP (10^{-4}M) significantly decreased intracellular Na^+ and probenecid this response to SNAP. Extracellular cGMP, which did not enter the cell, reduced intracellular Na^+. These results indicate that RPT cells contain soluble guanylyl cyclase and are able to synthesize cGMP in response to NO. These observations also strongly suggest that export of cGMP from the cell is required to inhibit apical Na^+ transport.

Taken altogether, the results indicate that natriuresis and P-N are mediated physiologically by RIcGMP.