Bartter Syndrome

Discuss the channels for regulation of electrolyte balance!

Bartter syndrome is caused by mutations of genes encoding proteins that transport ions across renal cells in the thick ascending limb of the nephron. Specifically, mutations directly or indirectly involving the Na-K-Cl cotransporter are key. The Na-K-Cl cotransporter is involved in electroneutral transport of one sodium, one potassium, and two chloride ions across the apical membrane of the tubule.

The basolateral calcium-sensing receptor has the ability to downregulate the activity of this transporter upon activation. Once transported into the tubule cells, sodium ions are actively transported across the basolateral membrane by Na+/K+-ATPases, and chloride ions pass by facilitated diffusion through basolateral chloride channels. Potassium, however, is able to diffuse back into the tubule lumen through apical potassium channels, returning a net positive charge to the lumen and establishing a positive voltage between the lumen and interstitial space. This charge gradient is obligatory for the paracellular reabsorption of both calcium and magnesium ions.

Proper function of all of these transporters is necessary for normal ion reabsorption along the thick ascending limb, and loss of any component can result in functional inactivation of the system as a whole and lead to the presentation of Bartter syndrome. Loss of function of this reabsorption system results in decreased sodium, potassium, and chloride reabsorption in the thick ascending limb, as well as abolishment of the lumen-positive voltage, resulting in decreased calcium and magnesium reabsorption. Loss of reabsorption of sodium here also has the undesired effect of abolishing the hypertonicity of the renal medulla, severely impairing the ability to reabsorb water later in the distal nephron and collecting duct system, leading to significant diuresis and the potential for volume depletion. Finally, increased sodium load to the distal nephron elicits compensatory reabsorption mechanisms, albeit at the expense of potassium by excretion by principal cells and resulting hypokalemia. This increased potassium excretion is partially compensated by ?-intercalated cells at the expense of hydrogen ions, leading to metabolic alkalosis.