KSN 2021
FULLY VIRTUAL MEETING
September 02 (Thu) - 05 (Sun)

Abstract Submission No. : 9160

Role of the NaCl cotransporter (NCC) in the regulation of Na+ and K+ balance in the kidney

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The NaCl cotransporter (NCC) is expressed in the apical membrane of the distal convoluted tubule (DCT) in the mammalian kidney that is upstream of the connecting tubule (CNT) and collecting duct (CD). In the DCT the salt reabsorption is electroneutral due to the 1:Na-1:Cl stoichiometry of NCC. In contrast, in the CNT/CD the Na^+ reabsorption occurs through the Na^+-channel ENaC and thus, is electrogenic and generates a negative potential in the lumen of the tubule that in turns, promotes the K^+ secretion, through the ROMK channels in the apical membrane. Thus, the more Na^+ that is reabsorbed, the more the K^+ that is secreted. In addition, the CNT/CD apical membrane also express the maxi BK channels that are activated by the share stress produced by the intra tubular fluid. Thus, the more the fluid delivery to CNT/CD, the more the potassium secretion. Because of this, the amount of salt reabsorption in the DCT helps to define the amount of K^+ secretion in the CNT/CD. If salt reabsorption is increased in DCT, the salt delivery to CNT/CD is reduced and thus K^+ secretion decreased, while decreased salt reabsorption in the DCT results in increased delivery to CNT/CD with the consequent increase in K^+ secretion. Thus, the DCT contains the potassium switch between salt reabsorption (and blood pressure) and potassium secretion.

The inherited or acquired disease of the DCT and CNT/CD demonstrate the relationship between salt reabsorption in DCT and K^+ secretion in CNT/CD. The Gitleman's disease due to inactivating mutations in the *SLC12A3* gene that encodes NCC and the SeSAME syndrome in with the *KCNJ10* gene that encodes the basolateral K^+ channel located in the DCT results in a similar renal phenotype of decreased blood pressure (due to reduced salt reabsorption) and hypokalemic metabolic alkalosis, own to the increased delivery of Na^+ and tubular fluid that promotes potassium secretion. In contrast, increased activity of NCC in the Familiar Hyperkalemic Hypertension (FHH), also known as Pseudohypaldosteronism type II or Gordon's syndrome results in hypertension (due to increased NaCl reabsorption) with hyperkalemia and metabolic acidosis, due to the decreased delivery of Na^+ and fluid to the CNT/CD, thus reducing the K^+ secretion. This relationship provides a mechanisms to explain the epidemiological observations that blood pressure levels in populations are associated with potassium ingestion. The higher the dietary potassium content, the lower

the blood pressure, because the kidneys promote salt excretion in order to get rid out of the excess of K^+. In contrast, the lower the dietary potassium, the higher the blood pressure because the kidneys will have to retain salt in order to prevent K^+ secretion. The discovery of the genes that when mutated produce FHH has allow us to elucidate a very fine molecular mechanism that modulates the potassium sensing by the DCT basolateral membrane together with the activation/inactivation of kinases and ubiquitin ligases that traduce the potassium content of the extracellular fluid in the corresponding NCC activity. If K^+ concentration is reduce, that is sensed by DCT cell increasing the activity of the kinases, which ultimately induce the activating phosphorylation of NCC. In contrast, increased K^+ concentration in extracellular fluid results in NCC inhibition. The precise nature of the kinases and ubiquitin ligases, as well as the mechanisms of their regulation will be discussed in the symposium.