

Aspects of renal sodium retention in puromycin induced nephrotic syndrome in rats

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ABSTRACT

Nephrotic syndrome (NS) is a renal disease due to protein-leaky glomerular basement membrane and characterized by proteinuria, hypoproteinemia and edema (sodium retention). Development of edema has been explained by the underfilling hypothesis: proteinuria is associated with hypoproteinemia and decreased plasma oncotic pressure and results in efflux of plasma water and hypovolemia with secondary activation of sodium retaining mechanisms. This is not always correct, so an overflow hypothesis has been proposed: proteinuria stimulates sodium re-absorption in the (cortical) collecting ducts leading to sodium overload and edema. The main luminal sodium transporter in this tubules segment is the epithelial sodium channel (ENaC). Regulation of ENaC may be through activation of mineralocorticoid receptor (MR) (e.g. aldosteron) or enzymatic activation from the luminal side by a newly identified enzyme, prostaticin.

The aims of the thesis were to investigate possible mechanisms for the development of sodium retention in puromycin aminonucleoside (PAN) induced NS in rats, equivalent to minimal change disease in humans; either through a) activation of MR or b) prostaticin-mediated stimulation of ENaC.

Activation of MR only had a minor but significant short-term impact on sodium homeostasis during development of NS. In urine from nephrotic rats prostaticin concentration was increased 22-fold concomitant with significantly decreased plasma concentration. Further, nephrotic urine induced a 4.5 fold increase in ENaC activity (patch clamp technique). This stimulatory effect of nephrotic urine was abolished by adding aprotinin (enzyme inhibitor) or 2 M amiloride (ENaC blocker) to nephrotic urine in vitro. The latter was corroborated by 72-hours low-dose amiloride treatment of nephrotic rats; urinary sodium output was equalized to control rats, and edema decreased significantly. This indicates that ENaC is "overactive" in NS.

In summary: For the first time we established that urinary prostaticin output was increased in NS and that nephrotic urine per se can stimulate ENaC activity. Further, short term blockade of ENaC with low-dose amiloride normalized renal sodium output and reduced the volume of edema significantly. Thus, development of sodium retention in relation to proteinuria may be the consequence of glomerular filtration of prostaticin which activates ENaC from the luminal side. This mechanism may well explain the link between proteinuria and sodium hyper-reabsorption suggested by the overflow hypothesis, and predicts a favourable effect of amiloride in treatment of edema in NS and other diseases with proteinuria (diabetes mellitus, preeclampsia etc).