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RENAL PHYSIOLOGY

HCO_3^- reclamation in the renal proximal tubule

> MCDL-NBCn2 mediates Na^+/HCO_3^- influx from the tubule lumen to the cytosol

Reclamation of HCO_3^- in the kidney has a key role in the regulation of systemic acid–base balance. Approximately 80% of HCO_3^- reclamation occurs in the proximal tubule and is thought to depend on the secretion of H^+ into the tubule lumen via the apical Na^+/H^+ exchanger NHE3 and the vacuolar-type H^+ pump. Now, Yi-Min Guo and colleagues report that HCO_3^- is also reclaimed via a direct pathway involving the electroneutral Na^+/HCO_3^- cotransporter NBCn2.

Previous studies in rat kidneys identified two full-length variants of NBCn2 that differ in their amino termini: MCDL-NBCn2 and MEIK-NBCn2. In their recent study, Guo *et al.* report that in the rat kidney, MEIK-NBCn2 is primarily expressed at the basolateral membranes of the medullary thick ascending limbs, whereas MCDL-NBCn2 is primarily expressed at the apical membranes of the proximal tubules. Based on this apical localization, they hypothesize that MCDL-NBCn2 mediates $Na^+/HCO3^-$ influx from the tubule lumen to the cytosol.

To investigate the physiological relevance of apical MCDL-NBCn2 expression, the researchers investigated the effects of systemic acid–base disturbances on the renal expression of MCDL-NBCn2 and NHE3 in rats. They found that 2 weeks of NH_4Cl-induced metabolic acidosis led to downregulation of MCDL-NBCn2 expression by ~31% and upregulation of NHE3 expression by ~97% compared with controls. Conversely, 2 weeks of metabolic alkalosis induced by $NaHCO_3$ overload led to a ~52% increase in MCDL-NBCn2 expression and ~46% decrease in NHE3 expression. Hypokalaemic alkalosis induced by potassium depletion for 2 weeks led to a decrease in MCDL-NBCn2 abundance by ~45% and an increase in NHE3 expression by ~121% compared with controls. These findings indicate an inverse relationship between the regulation of MCDL-NBCn2 and NHE3 expression.

"The [proximal tubule] reciprocally regulates MCDL-NBCn2 and NHE3 under conditions that require reciprocal modulation of HCO_3^- reclamation versus new HCO_3^- creation," state Guo *et al.* "Indeed, our mathematical simulations show that these two pathways, appropriately, have reciprocal efficiencies for HCO_3^- reclamation versus creation of new HCO_3^-. These predictions call for testing in future studies."

The researchers conclude that their findings are consistent with the hypothesis that proximal tubule apical membranes reabsorb HCO_3^- by two strategies. "The major one is the classic indirect CO_2 pathway, depending on H^+ secretion by the apical NHE3 and proton pumps. The minor one is the direct HCO_3^- pathway, in which NBCn2 transfers HCO_3^- across the apical membrane."

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ORIGINAL ARTICLE Guo, Y.-M. *et al.* Na^+/HCO_3^- cotransporter NBCn2 mediates HCO_3^- reclamation in the apical membrane of renal proximal tubules. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016080930 (2017)

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