

## Defective transport of acid-base equivalents in the kidney in syndromes of renal tubular acidosis

*Carsten A. Wagner*

Institute of Physiology and Center for Integrative Human Physiology, University of Zurich, Switzerland  
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The kidney plays a central role in maintaining and controlling systemic acid–base equilibrium in the extracellular space. Three processes contribute to renal control of acid–base balance: 1. reabsorption of filtered bicarbonate, 2. secretion of acid equivalents, mainly in the form of protons, and 3. synthesis and excretion of buffers, so-called titratable acids such as ammonia, facilitating proton excretion. The latter two processes generate also new bicarbonate replenishing bicarbonate used up by metabolism and acid-buffering.

Bicarbonate (re)absorption and acid secretion require the action of tightly regulated and coordinated transport proteins such as  $\text{Na}^+/\text{H}^+$ -exchangers,  $\text{Na}^+/\text{HCO}_3^-$ -cotransporters, V-type  $\text{H}^+$ -ATPases, and  $\text{Cl}^-/\text{HCO}_3^-$ -exchangers. Their importance is underlined by findings in patients with mutations in these genes causing metabolic acidosis as a consequence of impaired proximal or distal nephron function. Defective function of the basolateral proximal tubular  $\text{Na}^+/\text{HCO}_3^-$ -cotransporter NBCe1 (SLC4A4) causes bicarbonate wasting into urine (proximal renal tubular acidosis) and blindness which is due to its function also in the eye. In contrast, distal renal tubular acidosis (dRTA) can be the consequence of mutations in either the B1 (ATP6V1B1) or a4 (ATP6V0A4) subunits of the V-type  $\text{H}^+$ -ATPase in the acid-secretory type A intercalated cells. This type of dRTA is often associated with progressive sensorineural deafness as both

proteins are also expressed in the inner ear. An autosomal dominant variant of dRTA is caused by mutations in the chloride-bicarbonate exchanger AE1 (SLC4A1) which releases newly formed bicarbonate from type A intercalated cells into blood. Studies in AE1 deficient mice have allowed gaining more insights in the pathogenesis of this particular type of dRTA indicating that loss of functional AE1 protein causes also dysregulation of water channels with subsequent loss of the ability to concentrate urine. Moreover, it appears that AE1 is required for normal differentiation of type A intercalated cells both in man and mouse.

The main titratable acid, ammonia, is synthesized in the proximal tubule during metabolism of glutamine. Acidosis stimulates ammoniogenesis, a process that requires uptake of glutamine from blood occurring most likely via the basolaterally localized SNAT3 (SLC38A3)  $\text{Na}^+/\text{glutamine}$  cotransporter. Expression of SNAT3 is highly increased during acidosis. Altered expression of SNAT3 may be associated with chronic kidney disease often leading to metabolic acidosis.

The function of the aforementioned transport and metabolic pathways is tightly coordinated through only partially characterized mechanisms involving hormones such as angiotensin II, aldosterone, thyroid hormones, or endothelin. Insufficiency of aldosterone signalling is associated with distal renal tubular acido-

sis and hyperkalemia in man and mouse models. Aldosterone acts on several transport pathways involved in acid excretion in the renal collecting duct explaining some of the observed symptoms.

In addition, acquired syndromes of renal tubular acidosis due to i.e. autoimmune disease or side effects of drugs, have been less well characterized but available information suggests that dysregulation of acid-base transporters occurs and may explain at least in part the occurrence of metabolic acidosis.

Thus, loss of function of specific acid-base transporters as well as dysregulation due to lack of hormones or as side-effects of drugs and disease can cause various syndromes of renal tubular acidosis highlighting the physiological importance of these transport proteins and their regulators.

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Correspondence: Carsten Wagner  
Institute of Physiology,  
University of Zurich, Zurich, Switzerland  
E-mail: wagnerca@access.unizh.ch