Proximal RTA: Are all the charts completed yet?

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Renal tubular acidosis (RTA) is an uncommon disorder; however, the subgroup of isolated familial proximal RTA (pRTA) is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which in addition to acid excretion, other proximal tubular functions are impaired as well. In this issue of Nephrology Dialysis Transplantation, Katzir et al. [1] report findings in a single family with a specific form of isolated familial pRTA. It is highly likely that only very few physicians will ever encounter a case of this nature in their professional lives. Why then would this report be of interest?

The human body generates ~50–100 mmol of mineral acid per day. This load must be excreted, to prevent metabolic acidosis. Cells function best at physio-

logic pH; hence it is advantageous for the body to keep pH as constant as possible. The kidney is the only organ equipped to fully excrete the daily acid load, and the proximal tubule is the workhorse of that process. It transports hydrogen ion into the tubular lumen, reabsorbs bicarbonate (Figure 1) and contributes to the excretion of ammonium (NH$_4^+$) and titratable acid. The machinery consists of a number of integrated tools (Figure 1): a Na$^+$/H$^+$-ion exchange protein for hydrogen ion secretion (NHE-3) in the apical cell membrane; maintenance of a low intracellular sodium concentration by the activity of a basolateral Na$^+$/K$^+$/H$^+$-ATPase; a Na$^+$/HCO$_3^-$cotransporter in the basolateral membrane (kNBC-1) to facilitate translocation of bicarbonate to the extracellular fluid; carbonic anhydrases II and IV, which function in the disposition of CO$_2$ (Figure 1).

In the era of molecular biology, how does this model hold up? Are there inherited mutations of the transport proteins that confirm the model? This is indeed in part what was found. ‘Autosomal recessive pRTA with ocular abnormalities’ is, for instance, attributable to homozygous mutations in the gene for kNBC-1 (Figure 1) [2]. Affected patients show pRTA and short stature, glaucoma and cataracts, psychomotor delay and calcification of basal ganglia and

References:

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hyperamylasaemia. In addition to its expression in the renal proximal tubule, NBC-1 is also present in the epithelia of eye, brain and pancreas, which is likely to explain the diverse findings.

‘Sporadic isolated pRTA’ is a non-familial, transient pRTA observed in early childhood. Affected individuals present with pRTA, short stature and vomiting. Alkali therapy is helpful and the disorder disappears after a few years [3]. It is held that continued immaturity of kNBC-1 beyond the neonatal period is involved but disappears later in life.

‘ Autosomal dominant pRTA’ is a disorder of pRTA and short stature but no other abnormalities. It has thus far been described only once in nine members of a single family [4] over 20 years ago. Because of the kidney specific distribution of NHE-3 and based on a knock-out model of NHE-3 in mice [5], it was predicted that mutations of NHE-3 would be found, explaining autosomal dominant pRTA. However, the report by Katzir et al., in this issue of NDT, casts doubt on that proposal.

Katzir et al. [1] describe only the second family in the literature with autosomal dominant pRTA. The affected individuals had a pH in blood of 7.13, bicarbonate of 13.9 mmol/L, hyperchloremia and a low urinary pH of 5.4. An oral bicarbonate loading test partially corrected the metabolic acidosis, the urinary pH increased to 6.8 and the fractional excretion of bicarbonate rose to 22%. The findings were therefore the characteristic of pRTA. However, sequencing of genomic DNA from the patient and four affected family members failed to uncover mutations of NHE-3 and its regulatory proteins NHRF1 and NHRF2, nor were any mutations of other candidate genes (Figure 1) found.

What are the implications of these unexpected results? Is the technique or the concept at fault? The authors amplified and sequenced the coding areas and splice sites of the genes of interest. They also performed a haplotype analysis of introns and regulatory sequences of the candidate genes, using three to four microsatellite markers in each gene. If the reconstructed haplotypes were dissimilar between affected individuals, they were excluded as potential causes of the phenotypic defect. A lot of analysis must have been involved in this work; however, there may still be a possibility that three to four microsatellite markers are not sufficient to fully study the introns and the promoter area of a gene, or to exclude small changes such as a point mutation. It is notoriously difficult to completely exclude technical difficulty; we shall not know this with any certainty until more clusters of patients are studied.

What if our concept of obligatory proteins in pRTA (Figure 1) was deficient? Could there be transporters in pRTA that have been overlooked? The authors consider that a new enzyme or a regulatory factor related to the trafficking of NHE-3 might be involved. Indeed in the present work, the authors were unable to fully exclude the regulatory protein of NHE-3 NHRF1 from being involved. Given the limited phenotype of autosomal dominant pRTA and the kidney-specific distribution of NHE-3, they might conceivably be correct. Alternatively is it possible that a luminal H⁺-ATPase has a role in the human proximal tubule? In the rat it was shown that an apical vacuolar H⁺-ATPase contributed about one-third to bicarbonate reclamation in that segment [6]. Still other experiments in the salamander suggested the presence of tertiary active hydrogen ion secretion in the proximal tubule [7]. This mechanism utilizes an apical Na⁺-lactate and a basolateral membrane H⁺-lactate cotransporter. Finally bicarbonate has a paracellular backleak pathway into the tubular fluid in the late proximal tubule of the rat [8]. Could it become leakier than physiological and thus contribute to pRTA in humans?

Taken together, the inability of Katzir et al. to explain clear-cut pRTA in their patients on the basis of known transport mechanisms brings up the question as to whether other mechanisms could be involved and what they are. It will be exciting to see how this enigma unravels in the future.

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References


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