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Review Article

Renal tubular acidosis

*Gopal Basu**, *Golla Sudhakar*, *Anjali Mohapatra*

Department of Nephrology, Christian Medical College, Vellore 632004, Tamil Nadu, India

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ABSTRACT

Renal tubular acidosis is a collection of renal tubular disorders of diverse etiopathological states that present with hyperchloremic metabolic acidosis due to failure of net renal acid excretion. This review attempts to simplify the underlying physiological basis, the pathophysiological patterns, and the clinical manifestations. An algorithmic approach to diagnose RTA along with a description of most of the tests used is provided. The clinical approach to RTA is followed by a brief note on its therapy.

1. Introduction

Renal tubular acidosis is a collection of renal tubular disorders of diverse aetiolopathological states that present with hyperchloremic metabolic acidosis due to failure of net renal acid excretion. Renal acid excretion is impaired by an inability either to conserve bicarbonate or to excrete the H^+ ions. Renal tubular acidosis (RTA) commonly manifest with polyuria, polydipsia, renal calculi, failure to thrive, growth retardation, and musculoskeletal abnormalities. First described in 1935,[1] it was confirmed as a renal tubular disorder in 1946.[2] The term "renal tubular acidosis" was designated in 1951.[3] The disease most often affects children, making it imperative to diagnose and treat it effectively to preserve growth potential and prevent ill-effects of systemic metabolic acidosis. In this article we review the pathophysiology and clinical approach to RTA, with a brief note on its therapy.

2. Physiologic renal handling of acid base balance

The average H^+ generated by the adult diet amounts to 50–100 mmol/day (0.75–1.5 mmol/kg body weight) and this daily load is excreted by the kidney. The mechanisms of acid excretion vary by tubular segment. Firstly, the necessity to excrete a net acid load indicates the need for all of the filtered bicarbonate (4500 mmol/day) to be reabsorbed. Secondly, excretion of 50–100 mmol/day of acid as free H^+ ions would result in lowering the urine pH to 1.0. As the lowest physiological urine pH is ~4.2, and the average urine pH is 6.0, the excretion of H^+ ion is aided significantly by luminal buffering. The quantitatively important buffering agents in the renal tubule (other than bicarbonate) include ammonia and phosphate. The net effect of secretion of each H^+ ion is associated with the generation of one HCO_3^- ion in the plasma.

* *Corresponding author*. Tel.: +91 41 62282053; fax: +91 41 62232035.
E-mail addresses: drbasug@yahoo.co.in, drbasug@cmcvellore.ac.in (G. Basu).
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Conversely, with every HCO_3^- lost in the urine, there is addition of one H^+ ion to the plasma, reducing the net acid excreted. Thus, the net acid excretion by a normal individual in urine is expressed by the equation:

$$NAE = ([TA] + [NH_4^+]_U - [HCO_3^-]_U \times V)$$

where NAE is the net acid excretion, TA is titrable acidity, and the urine V is the urine flow rate.

The titrable acidity is defined as the acid load excreted (predominantly by phosphate buffer) and determined by the amount of alkali required to bring the urine pH to 7.4.

While on a standard diet, the usual bicarbonate excretion is negligible, NH_4^+ excretion is 50–60 mmol/day (about 15% of maximum capacity) and titrable acidity is 20–30 mmol/day (about 40% of maximum capacity).[4] In systemic acidosis of non-renal origin, the net acid excretion can exceed 300 mmol/day, primarily by an enhanced NH_4^+ secretion and subsequent reduction in pH of the urine. During alkalosis, the net acid excretion can become negative, by increasing the quantity of HCO_3^- lost in urine, thereby increasing the urine pH. These changes are considered "appropriate" responses of kidney in the respective acid base disturbances.

Proximal tubular acidification of urine is achieved predominantly by bicarbonate reabsorption and to a small extent acid secretion. The PCT reclaims up to 80–85% of filtered bicarbonate (~4300 mmol per day), thereby contributing to the reduction in the final bicarbonate concentration in urine to negligible amounts. The major players in PCT bicarbonate reabsorption are luminal Na^+/H^+ exchanger (NHE3), brush border carbonic anhydrase IV (CA-IV), cytoplasmic carbonic anhydrase II (CA-II), basolateral Na^+-$3HCO_3^-$ cotransporter (NBC1) and the Na^+/K^+ ATPase. The negative potential generated by low intracellular sodium concentration due to the Na^+/K^+ ATPase activity, favors sodium reabsorption which is coupled to H^+ secretion by the NHE3. Two-thirds of PCT H^+ secretion is by NHE3 while the rest one-third is by the H^+ ATPase on the luminal side.[5,6] The secreted H^+ combines with luminal HCO_3^- with help of luminal CA-IV forming carbon dioxide and H_2O. CO_2 diffuses into the PCT cell through the luminal membrane and is rehydrated by the cytosolic enzyme CA- II, to re-form H^+ and HCO_3^-, thus effectively transporting the HCO_3^- from the tubular lumen into the cell. The HCO_3^- is then reabsorbed in to the systemic circulation along with Na^+ ions by the basolateral Na^+-$3HCO_3^-$ cotransporter, (NBC1). Thus proximal tubular acidification is closely linked to Na^+ reabsorption. However Na^+ reabsorption in PCT could also be independent of HCO_3^- reabsorption, via the multiple co-transporters that transport Na^+ into the cell along with glucose or phosphate or citrate or amino acids. PCT acidification by HCO_3^- reabsorption is influenced by various mechanisms. Higher luminal HCO_3^- concentration and higher luminal PCO_2 increase proximal Na+ and HCO_3^- reabsorption, while increased peritubular HCO_3^- concentration reduces it. Lower extracellular fluid volume, α-adrenergic stimulation & renin angiotensin aldosterone activation increases NHE3 activity and proximal reabsorption. A similar effect is noticed with glucocorticoids. Higher parathormone (PTH) level increases luminal electro-positivity, stimulating Na^+ and HCO_3^- reabsorption. Fig. 1 depicts the various mechanisms of proximal acidification in the PCT.

In addition to the bicarbonate reclamation and acid secretion, PCT cell also helps in synthesis and secretion of the ammonium (NH_4^+), which forms the source of ammonia (NH_3) buffer for the distal acidification at the collecting tubule. NH_4^+ is generated in the PCT by metabolism of glutamine (to glutamate) and is secreted into the tubular lumen by the NHE3, as the NH_4^+ is transported by binding to the H^+ binding site on this exchanger. Increased ammonium production and secretion serves to buffer and mop up excessive acid secreted by the

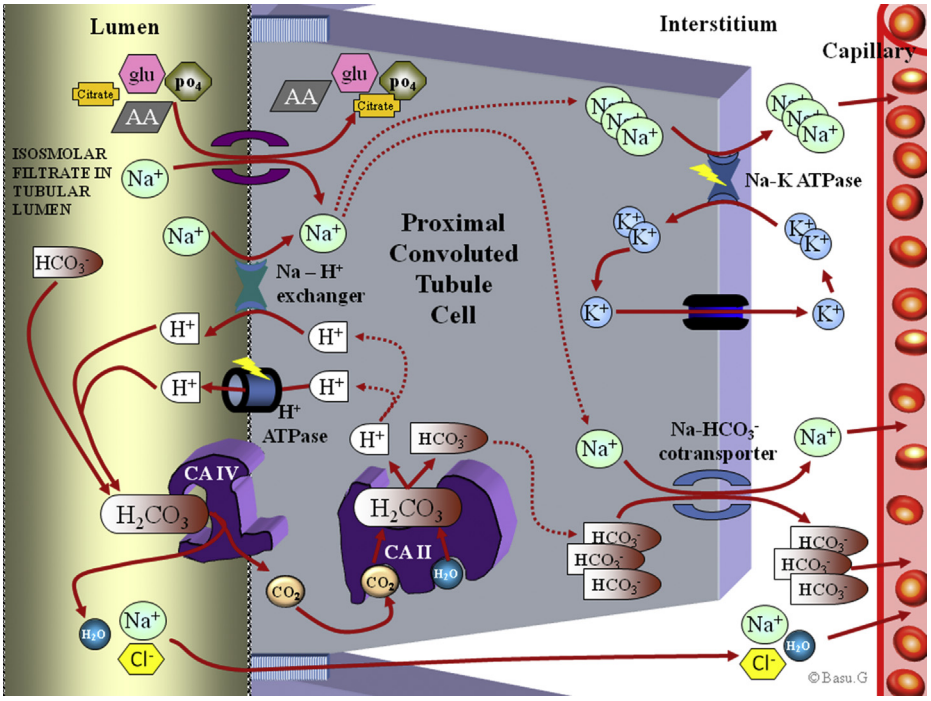

Fig. 1 – Proximal Tubular Cell pathways of acidification.