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Carbonic Anhydrase Activity And Renal Tubular Acidosis

Manopriya T, Bhaskaran K and Dhastagir Sultan Sheriff,
Anna Medical College, Mauritius

Abstract
Carbonic anhydrase (CA) is a group of zinc containing metallo-enzymes involved in the formation and breakdown of carbonic acid from carbon di oxide and water. The release of proton helps to maintain acid-base balance in blood and other tissues. Of the various iso-enzymes known CA II is one of the most catalytically active form present in most tissues including erythrocytes.
CA II plays a major role in renal regulation of acid/ base homeostasis. It is involved in osteoclast-mediated bone desorption. An autosomal recessive syndrome with CA II deficiency is found mostly in the Middle East and Mediterranean regions. The deficiency syndrome results in rental tubular acidosis (RTA), osteopetrosis and cerebral calcification.
Key words: *Carbonic Anhydrase (CA), isoenzymes, Renal Tubular Acidosis (RTA)*

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I. Introduction

One of the ubiquitous enzymes Carbonic anhydrase plays an important role in human health and disease. The reaction it catalyzes is reversible which is involved in the formation and breakdown of carbonic acid. [1]

$CO_2 + H_2O \leftrightarrows H_2CO_3$

The enzyme is classified into four groups depending upon its cellular location.
Cytosolic (CA I,II,III,VII,XIII); mitochondrial (CA VA,VB); secretory (CAVI) ; membrane associated (CA IV, IX,XII,XIV,XV).

Isoforms of the enzyme differ in their respective enzyme activities and mode of inhibition. Membrane bound enzymes are glycoproteins with the histidine moiety required for its catalytic functions. CA IV is not a glycoprotein. [2-3]

CA IV the membrane associated enzyme structure is fully elucidated. Its mutation say in the leader sequence or in the body may cause retinitis pigmentosa-17(RP-17). It is also reported to be a tumor suppressor gene. CAs role in renal physiology and its pathological conditions require a reflection and introspection.

CA II is one of the most widespread of the CA isozymes and also the one with the highest catalytic activity.[2-3]It is a cytoplasmic isozyme expressed in a variety of cell types in different tissues. The physiological functions of CA II include pH regulation, CO2 and HCO3 transport, and maintaining H2O and electrolyte balance. [4] The only known inherited deficiency of a carbonic anhydrase of clinical significance is the CA II deficiency syndrome (MIM# 259730), which is inherited as an autosomal recessive trait.[4] The clinical manifestations include osteopetrosis, renal tubular acidosis, and cerebral calcification. Additional clinical features of the disease include developmental delay, short stature, and a history of multiple skeletal fractures by adolescence, and cognitive defects varying from mild learning disabilities to severe mental retardation.

Carbonic anhydrase II (CAII) is soluble and is expressed along the nephron with the exception of the thin ascending limb [5]. It is expressed in the distal nephron's intercalated cells which facilitates the excretion of proton. This action is manifested with a physical and functional interaction with an **anion exchanger 1 (AE1**), named as transport metabolon. [6] CAII may also participate in sodium reabsorption. It may do so by binding to NHE3 and NBCe1 from the filtrate via the provision of substrate.[7-8]

Renal tubular acidosis is due to defects in the renal regulation of Blood pH which may be due to reabsorption of bicarbonate or due to acidification of urine. There are four types of RTA

II. Renal regulation of acid base balance can be divided into two major phases:

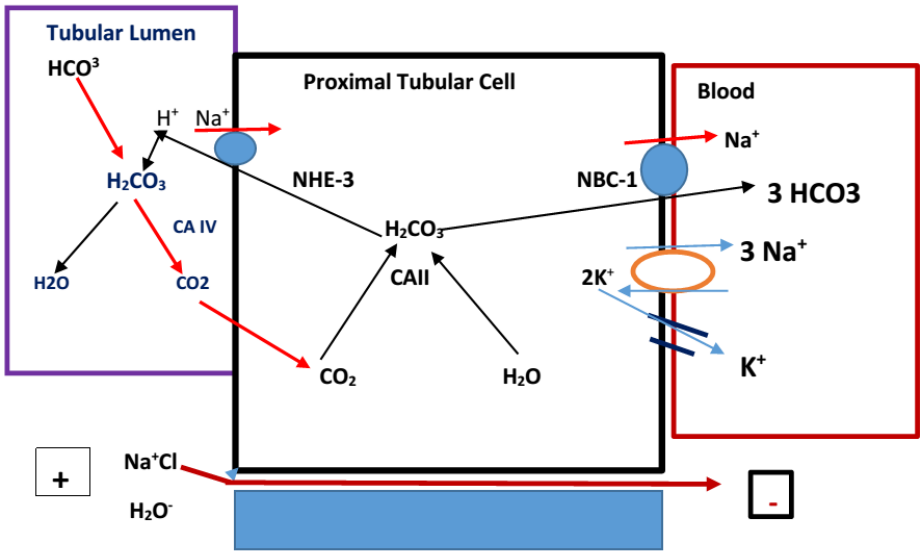
In the proximal tubule the filtered bicarbonate reabsorption depends upon carbonic anhydrase activity and several transporters:

Carbonic anhydrase (CA-II) present inside the cell catalyzes the formation carbonic acid by acting on water and carbon di oxide. The carbonic acid formed ionizes to form hydrogen ion and bicarbonate. The bicarbonate formed is transported into the blood along with sodium with the help of cotransporter **NBC-1**.[7]

The newly formed hydrogen ion formed is excreted by the tubule by **NHE-3** (The **sodium/proton exchanger isoform** 3 **(NHE3)** driven by anti-transport sodium down its concentration gradient.

Intraluminal bicarbonate combines with hydrogen to form water and carbon di oxide by the action of carbonic anhydrase (IV). Water and carbon di oxide formed in the lumen diffuses back to the cell which form the substrates for CA-II which drives a net absorption of bicarbonate.

Fig.1.Diagrammatic Representation of Reabsorption of Bicarbonate in the Proximal Tubule



NHE-3- sodium/proton exchanger isoform 3 **NBC-I**-sodium-bicarbonate co transporter 1
CA- carbonic Anhydrase

The acidification of urine by the distal tubule depends on:

The secretion of ammonia in the proximal tubule and the continued absorption of bicarbonate within the loop of Henle along with secretion of hydrogen ions by the alpha intercalated cell in the cortical portion of the collecting duct play an important role. (secretion of hydrogen ions is sensitive to the action of aldosterone).

The secretion of ammonia in the proximal tubule plays particularly an important role in renal acid-base homeostasis.

Ammonia represents the primary buffer for the excreted hydrogen ions. Secreted phosphate provides a buffer as well.

The alpha-intercalated cells play the largest direct role in the acidification of urine, which occurs via the following mechanisms:

Carbonic anhydrase (CA-II) creates carbonic acid which ionizes to form bicarbonate and a hydrogen ion, in a mechanism similar to that which occurs in the proximal tubule.

Bicarbonate ion is transported into the blood by the by the chloride-bicarbonate anti-porter AE1

The resulting hydrogen ion is transported into the lumen by the vacuolar H^+-ATPase and the H^+-K^+-ATPase, with the vacuolar H+-ATPase playing the dominant role.

Ammonia and phosphate buffer the secreted hydrogen ions

Note: there is no luminal carbonic anhydrase to drive the re-uptake of CO2, unlike in the proximal tubule

There are four types of Renal Tubular Acidosis: [8-12]

1. Distal tube RTA- Type I
2. Proximal RTA- Type II
3. Mixed RTA - Type III
4. Hypoaldosterenism- Type IV

Distal RTA I:

A decreased secretion of hydrogen ions by the distal tubule in response to increased acidification of the serum is the cause for RTA I which may be due to congenital genetic variants of ion transport protein and acquired due to immunological destruction of alpha-intercalated cells

Proximal RTA- Type II

It is due to reduced reabsorption of bicarbonate in the proximal tubule. It may be due to defect in the secretory capacity of renal tubules cells to maintain a low intracellular sodium. Such a defect is seen in Fanconi syndrome. Fanconi syndrome can be secondary to cystinosis, galactosemia or tyrosinemia. It may be due vitamin D deficiency or Sjogren syndrome or drug induced following the intake of valproic acid or aminoglycosides. Type III and Type IV are secondary to defects in proximal and distal tubules or due to aldosterone deficiency.

The carbonic anhydrase II (CA II) deficiency syndrome is an autosomal recessive disorder that produces osteopetrosis, renal tubular acidosis, and cerebral calcification. Other features include developmental delay, short stature, cognitive defects, and a history of multiple fractures by adolescence

A child with RTA may be associated with nephrolithiasis, nephrocalcinosis, rickets, osteromalacia, hyperammonemia and hyperkalemia in Type I RTA. Patients with TYPE II may have glucosuria, aminoaciduria and hypophosphatemia (Fanconi syndrome). In Type IV the patients may be hyperkalemic.

Differential diagnosis of different RTA types is based on the measurements of :
Anion gap, Serum Potassium levels, Early morning urine pH

Table.1. Summary of Laboratory Evaluation in Renal Tubular Acidosis patients

Laboratory Evaluation	RTA Type II	RTA Type I	RTA Type IV
Serum potassium	Normal mostly	Normal mostly	increased
Urine pH	<5.5	>5.5	<5.5
Urine anion gap	-	+	+
Fractional potassium secreted	Normal/+	+/-	Normal mostly/+
Calcium excreted	Normal	+	Normal
Citrate excreted	Normal	+	Normal
Nephrocalcinosis	-	+	-

III. Conclusion:

Carbonic anhydrase and its isoenzymes are involved in the formation and breakdown of carbonic acid. Carbonic anhydrase play a very important role in the kidney's metabolic regulation of Blood pH, particularly CA II and CA IV. CA II deficiency syndrome delineates how important is CA activity in renal regulation of Blood pH.

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