SCHOOL OF MEDICNE AND HEALTH SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

PBL SEMINAR

KIDNEY FUNCTION – PART 11

- The kidney is a vital organ and humans cannot survive without at least one kidney.
- The Nephrons are the functional units of the kidney.

What are some of the basic functions of the Kidneys?

- The kidneys regulate Extracellular Fluid (ECF) Volume and Electrolyte composition to compensate for wide daily variations in Water and Electrolyte intake.
- The kidneys form urine in which the potentially toxic waste products of metabolism are excreted.
- The kidney utilizes three processes to form urine: Glomerular Filtration, Tubular Reabsorption and Tubular Secretion
- Filtration is accomplished due to the Hydrostatic pressure of blood.
- The Glomerular Filtration Rate (GFR) of both kidneys is about 180L per day.
- Most of the fluid in the Glomerular filtrate are reabsorbed and returned to the vascular system to maintain blood volume and pressure.
- The Glomerular Filtrate contains all the low molecular weight molecules found in plasma in essentially the same concentration (Glucose, Urea, Uric acid, Amino Acids, Electrolytes etc.).
- Large molecules, such as Proteins, and Blood Cells are not filtered.
- As the Glomerular filtrate travels through the Nephron, most of its components are reabsorbed to varying degrees, depending on the need to adjust blood composition and the ability of the kidney to reabsorb nutrients and other molecules.
- The kidneys play major role in the excretion of products of Protein and Nucleic acid metabolism – such as Urea, Creatinine, Creatine, Uric acid, Sulphate and Phosphate

What are some of the regulatory functions of the kidneys?

The regulatory functions of the kidneys include the following:

- Regulation of water:
  - The hormone called Arginine Vasopressin (AVP) produced by the Posterior Pituitary acts on the kidney tubules causing reabsorption of water from the glomerular filtrate.
- Regulation of Electrolyte:
  - The hormone Aldosterone acts on the kidney tubules causing the reabsorption of Sodium ions (Na^+) in exchange for the secretion of Potassium ions (K^+) and Hydrogen ions (H^+).
- Regulation of Acid-base balance:
  - This involves maintaining the pH (acidity/alkalinity) in blood and other body fluids.

How does the kidney regulate Acid-Base balance?

- The kidney regulates acid-base balance by controlling:
  - Re-absorption of Bicarbonate ions (HCO_3^-)
  - Secretion of Hydrogen ions (H^+).

- Both processes depend on formation of Bicarbonate ions (HCO_3^-) and Hydrogen ions (H^+) from CO_2 and H_2O within the Tubule cells in the kidney.

$$CO_2 + H_2O \xleftrightarrow{\text{Carbonic Anhydrase}} H_2CO_3 \xleftrightarrow{} H^+ + HCO_3^-$$

- The H^+ formed in this reaction is actively secreted into Tubule fluid in exchange for Na^+.
- The kidney plays important role in eliminating the Acids by the following mechanisms:
  - Re-absorption of Sodium Bicarbonate (alkali) by Proximal Renal Tubules,
  - Regeneration of Bicarbonate (HCO^-_3) by Distal Renal Tubules
  - Production of Ammonia (NH_3) by Distal Renal Tubules, which secrete H^+ ions and maintain a gradient of H^+ ions between cell and lumen.

Schematic diagrams representing these processes are presented in the Figures below:

All aspects of renal involvement in Acid Base balance are interlinked, but for clarity are dealt with separately below.

TAKE NOTE:

- All the H^+ ions, which are buffered in the blood during metabolism, must eventually be excreted from the body via the kidneys, regenerating the HCO_3^- ions used up in the buffering process and maintaining the plasma HCO_3^- concentration within normal limits.
- Secretion of H^+ ions by the Tubular cells serves initially to reabsorb HCO_3^- ions from the Glomerular filtrate so that they are not lost from the body.
- When all the HCO_3^- ions have been recovered (reabsorbed), any deficit due to the buffering process is regenerated.
- It is important to note that the mechanism for Reabsorption of HCO_3^- ions is different from the mechanism for the Regeneration of HCO_3^- ions. (See differences in diagrams below).

How are the Bicarbonate ions (HCO_3^-) in the Glomerular Filtrate Reabsorbed (Reclaimed or Recovered)?

- Bicarbonate ions (**HCO_3^-**) are freely filtered by the Glomerulus.
- The concentration of **HCO_3^-** ions in the Tubular fluid is equivalent to that of Plasma.
- If **HCO_3^- ions** were not reabsorbed in the Renal Tubules the Buffering Capacity of Blood plasma would be depleted rapidly.
- The process of reabsorption of **HCO_3^-** occurs mostly in the Proximal Convoluted Tubule and is summarised in **Figure 1**.
- In the Tubular Lumen HCO_3^- ions filtered through the Glomerulus combine with H^+ ions secreted from the Tubular cell forming Carbonic Acid (H_2CO_3).

- The H_2CO_3 is then converted to CO_2 and H_2O in a reaction catalysed by the enzyme Carbonic Anhydrase, which is present in the brush border of the renal tubular cells.
- The CO_2 produced readily crosses into the Tubular cell down a concentration gradient.

- Inside the Tubular cell the CO_2 interacts with H_2O again, to form H_2CO_3 in a reaction catalysed by the same enzyme, Carbonic Anhydrase.
- The H_2CO_3 then dissociates to form HCO_3^- ions and H^+ ions.
- The HCO_3^- ions formed diffuse into the blood stream whilst the H^+ ions are transported into the Tubular Lumen in exchange for Na^+ ions.
- In this way, virtually all the HCO_3^- ions in the Glomerular Filtrate are Reabsorbed or Reclaimed.

How are the Bicarbonate ions Regenerated?

- After the process of reabsorption of the HCO_3^- ions is completed, the process of regeneration compensates for any deficit in the amount of HCO_3^- reabsorbed.
- The mechanisms for reabsorption of HCO_3^- ions and for the regeneration of HCO_3^- ions different.
- These two processes are very similar and are sometimes confused.
- The process of Regeneration of HCO_3^- is presented in Figure 2.

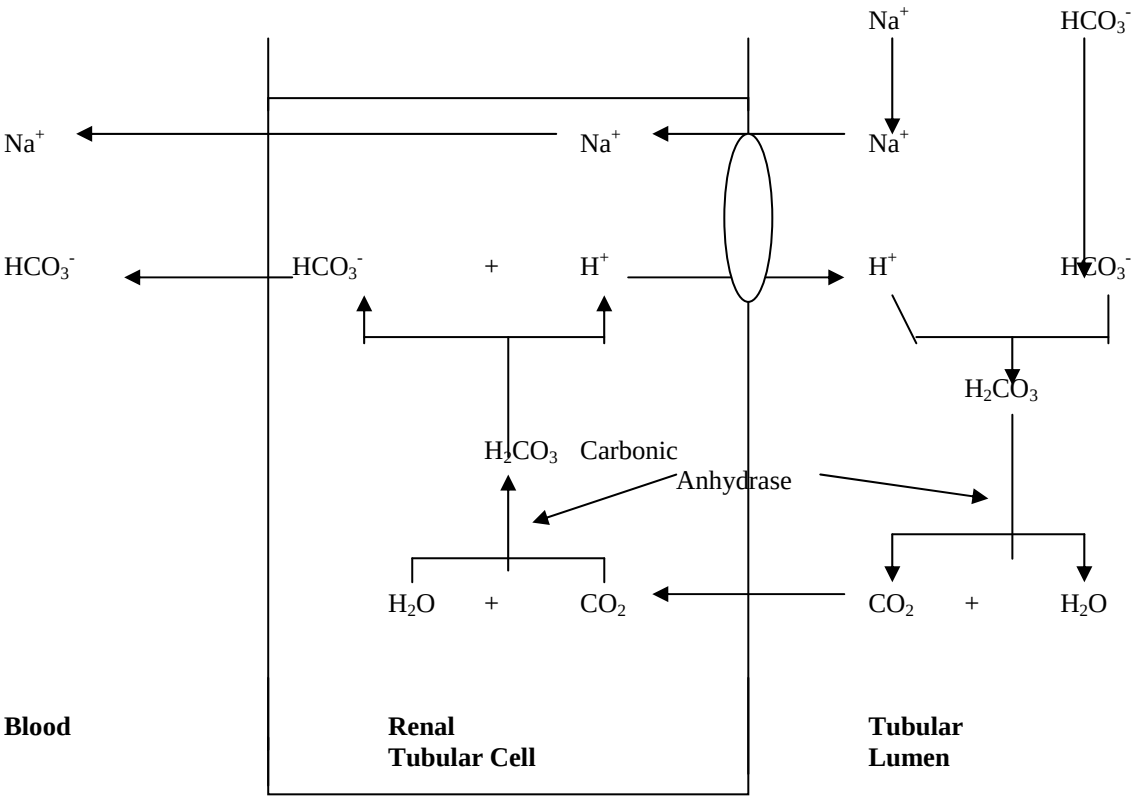
How are Hydrogen ions (H^+) excreted by the Renal Tubules?

- The H^+ ions are secreted in exchange for Na^+ ions.
- The energy for this exchange comes from the Na^+ - K^+ -ATPase (Sodium-Potassium pump) that maintains the concentration gradient for Na^+ ions.
- Hydrogen ions (H^+) are secreted by buffers
- The predominant buffers in the Urine are Phosphate (HPO_4^{2-}) and Ammonium (NH_3).
- Phosphate is freely filtered by the Glomerulus and passes down the Tubule where it combines with H^+ ions to form $H_2\ PO_4^-$. (**Figure 3**)

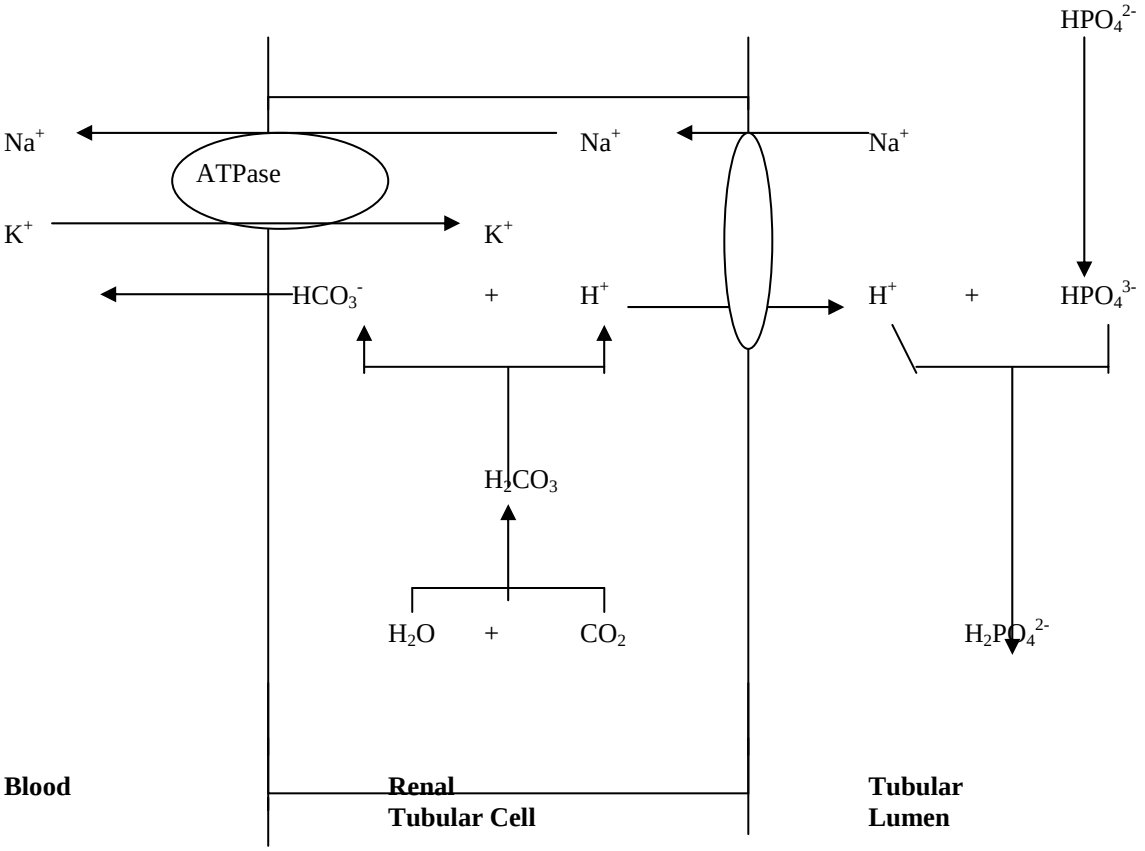
- Ammonia (NH_3) is produced in Renal Tubular cells by the action of the enzyme Glutaminase on the Amino acid Glutamine.
- This enzyme functions optimally at a lower (more acidic) than normal pH.
- More Ammonia is produced during Acidosis thus improving the buffering capacity of the Urine.
- Ammonia is un-ionised and so rapidly crosses into the Renal Tubular Lumen down its concentration gradient.
- In the Tubular Lumen the NH_3 combines with H^+ ions to form the NH_4^+ ions (Ammonium ions), which being ionised does not pass back into the tubular cell.
- The NH_4^+ ions are therefore lost in the urine, along with the H^+ ions it contains. (**Figure 4**).

Figure 5 shows Schematic representation of the process of reabsorption and pH regulation in the Proximal and Distal sections of the Renal Tubule.

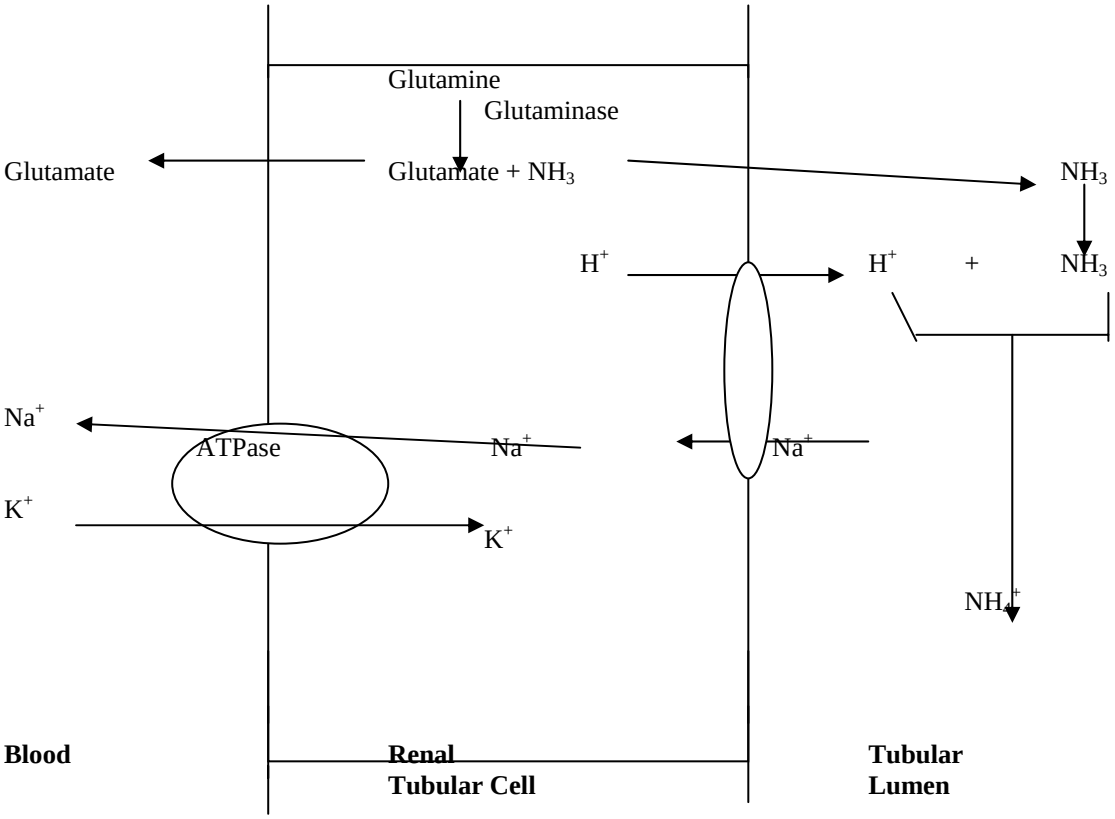
REABSORPTION OF HCO_3^- BY RENAL TUBULAR CELLS



PHOSPHATE BUFFERING IN THE RENAL TUBULE



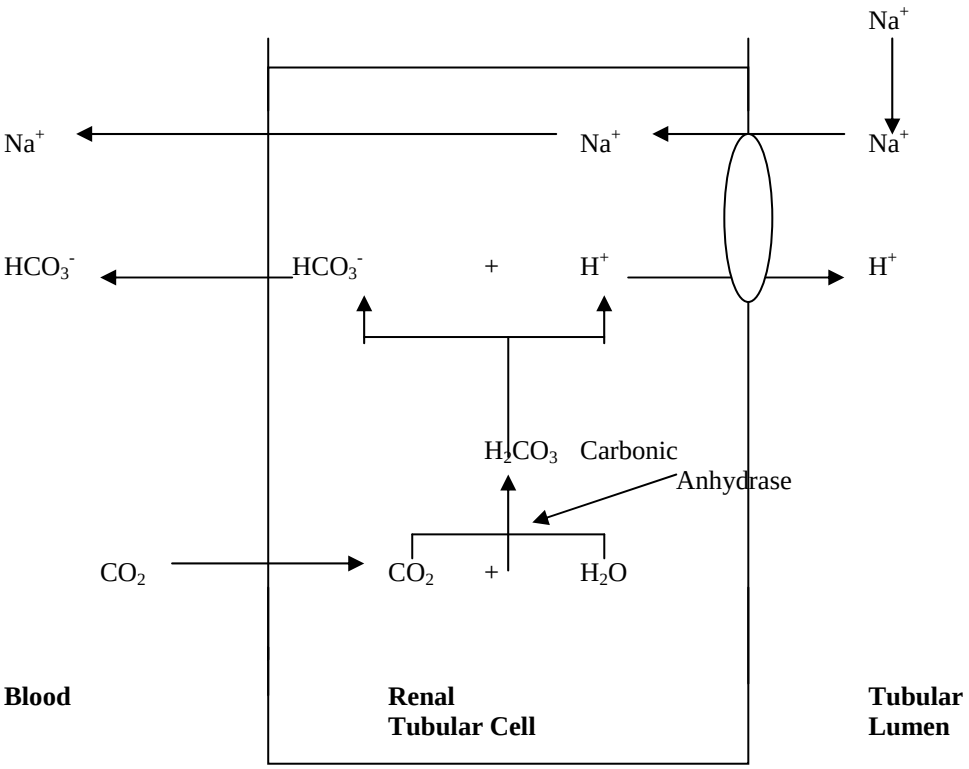
AMMONIA BUFFERING IN THE RENAL TUBULE



It must be noted that all the H^+ ions, which are buffered in the blood during metabolism must eventually be excreted from the body via the kidneys, regenerating the HCO_3^- ions used up in the buffering process and maintaining the plasma HCO_3^- concentration within normal limits.
Secretion of H^+ ions by the tubular cells serves initially to reabsorb HCO_3^- ions from the glomerular filtrate so that they are not lost from the body.

When all the HCO_3^- ions have been recovered, any deficit due to the buffering process is regenerated.
The mechanisms for re-absorption of HCO_3^- ions and for the regeneration of HCO_3^- ions are very similar and are sometimes confused (See differences in diagrams below).

REGENERATION OF HCO_3^- AND EXCRETION OF H^+ BY RENAL TUBULAR CELLS



It should be noted that the excreted H^+ ions must be buffered in urine or the H^+ ion concentration would rise to very high levels.
Phosphate acts as one of such buffers in the urine, while Ammonia is another.