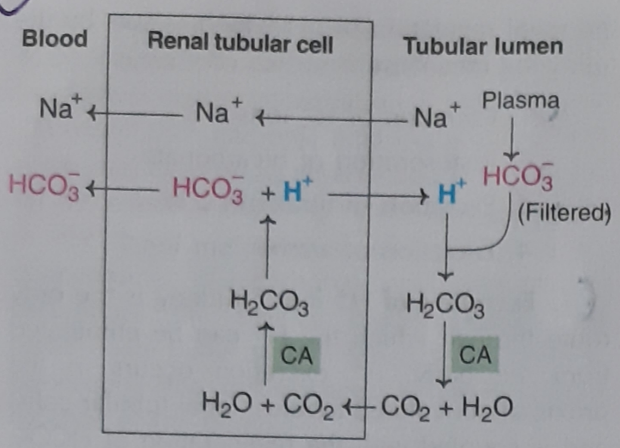

Fig. 21.6 : Renal regulation of blood pH–Reabsorption of bicarbonate (CA–Carbonic anhydrase).

Bicarbonate freely diffuses from the plasma into the tubular lumen. Here HCO_3^- combines with H^+, secreted by tubular cells, to form H_2CO_3. H_2CO_3 is then cleaved by carbonic anhydrase (of tubular cell membrane) to form CO_2 and H_2O. As the CO_2 concentration builds up in the lumen, it diffuses into the tubular cells along the concentration gradient. In the tubular cell, CO_2 again combines with H_2O to form H_2CO_3 which then dissociates into H^+ and HCO_3^-. The H^+ is secreted into the lumen in exchange for Na^+. The HCO_3^- is reabsorbed into plasma in association with Na^+. Reabsorption of HCO_3^- is a cyclic process with the net excretion of H^+ or generation of new HCO_3^-. This is because the H^+ is derived from water. This mechanism helps to maintain the steady state and will not be effective for the elimination of H^+ or generation of new HCO_3^-.

3. **Excretion of titratable acid :** Titratable acidity is a measure of ***acid excreted into urine*** by the kidney. This can be estimated by titrating urine back to the normal pH of blood (7.4). In quantitative terms, titratable acidity refers to the number of milliliters of N/10 NaOH required to titrate 1 liter of urine to pH 7.4. Titratable acidity reflects the H^+ ions excreted into urine which resulted in a fall of pH from 7.4 (that of blood). The excreted H^+ ions are actually buffered in the urine by phosphate buffer as depicted in ***Fig.21.7***, and briefly described hereunder.

As already discussed, H^+ ion is secreted into the tubular lumen in exchange for Na^+ ion. This Na^+ is obtained from the base, disodium hydrogen phosphate (Na_2HPO_4). The latter in turn combines with H^+ to produce the acid, sodium dihydrogen phosphate (NaH_2PO_4), in which form the major quantity of titratable acid in urine is present. As the tubular fluid moves down the renal tubules, more and more H^+ ions are added, resulting in the acidification of urine. This causes a fall in the pH of urine to as low as 4.5. Any further fall in the pH will cause depletion of Na^+ ions.

4. **Excretion of ammonium ions :** This is another mechanism to buffer H^+ ions secreted into the tubular fluid. The H^+ ion combines with

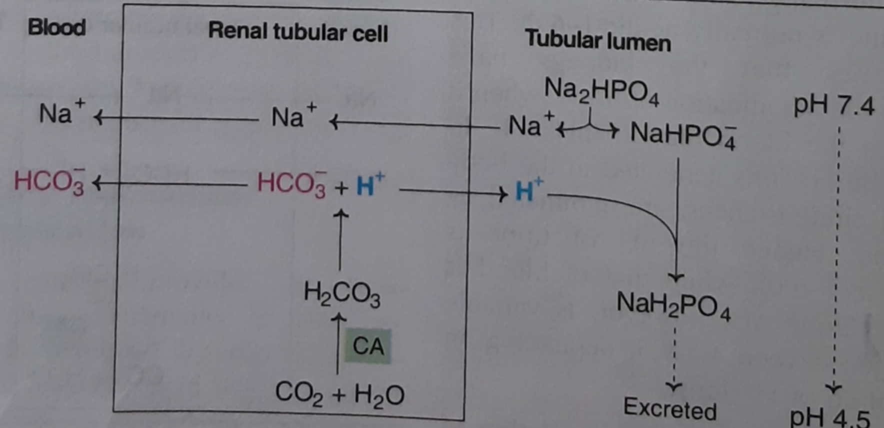

Fig. 21.7 : Renal regulation of blood pH–Excretion of titratable acid by phosphate buffer mechanism (CA–Carbonic anhydrase).

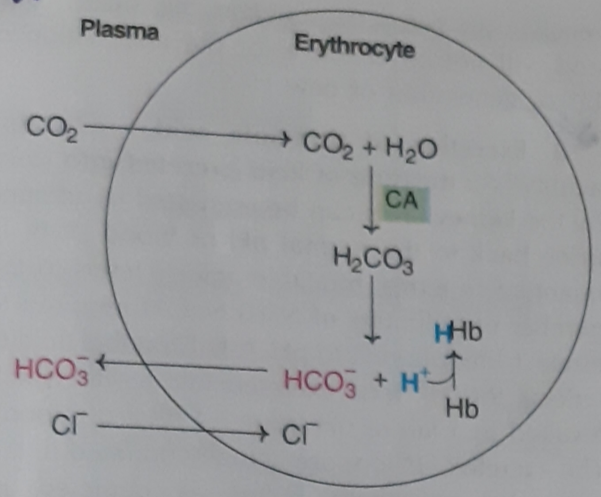

Fig. 21.4 : Generation of bicarbonate by the erythrocyte (CA–Carbonic anhydrase; Hb–Hemoglobin).

III. Renal mechanism for pH regulation

The role of kidneys in the maintenance of acid-base balance of the body (blood pH) is highly significant. The ***renal mechanism*** tries to provide a ***permanent solution to the acid-base disturbances.*** This is in contrast to the temporary buffering system and a short term respiratory mechanism, described above.

The kidneys regulate the blood pH by maintaining the alkali reserve, besides excreting or reabsorbing the acidic or basic substances, as the situation demands.

Urine pH normally lower than blood pH : The pH of urine is normally acidic (~***6.0***). This clearly indicates that the kidneys have contributed to the acidification of urine, when it is formed from the blood plasma (pH 7.4). In other words, the H^+ ions generated in the body in the normal circumstances, are eliminated by acidified urine. Hence the pH of urine is normally acidic (~6.0), while that of blood is alkaline (7.4). Urine pH, however, is variable and may range between 4.5-9.5, depending on the concentration of H^+ ions.

Carbonic anhydrase and renal regulation of pH : The enzyme carbonic anhydrase (inhibited by ***acetazolamide***) is of central importance in the renal regulation of pH which occurs by the following mechanisms.

1. Excretion of H^+ ions
2. Reabsorption of bicarbonate
3. Excretion of titratable acid
4. Excretion of ammonium ions.

1. Excretion of H^+ ions : Kidney is the only route through which the H^+ can be eliminated from the body. H^+ excretion occurs in the proximal convoluted tubules (renal tubular cells) and is coupled with the regeneration of HCO_3^-. The process depicted in *Fig.21.5*, occurs as follows.

Carbonic anhydrase catalyses the production of carbonic acid (H_2CO_3) from CO_2 and H_2O in the renal tubular cell. H_2CO_3 then dissociates to H^+ and HCO_3^-. The H^+ ions are secreted into the tubular lumen in exchange for Na^+. The Na^+ in association with HCO_3^- is reabsorbed into the blood. This is an effective mechanism to eliminate acids (H^+) from the body with a simultaneous generation of HCO_3^-. The latter adds up to the alkali reserve of the body. The H^+ combines with a non-carbonate base and is excreted in urine.

2. Reabsorption of bicarbonate This mechanism is primarily responsible to conserve the blood HCO_3^-, with a simultaneous excretion of H^+ ions. The normal urine is almost free from HCO_3^-. This is explained as follows (***Fig.21.6***).

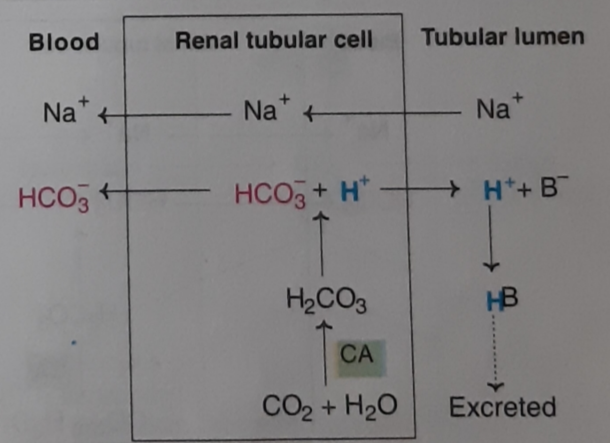

Fig. 21.5 : Renal regulation of blood pH–Excretion of H^+ ions (CA–Carbonic anhydrase).

It is evident that at a blood pH 7.4, the ***ratio of bicarbonate to carbonic acid is 20 : 1***. Thus, the bicarbonate concentration is much higher (20 times) than carbonic acid in the blood. This is referred to as ***alkali reserve*** and is responsible for the effective buffering of H^+ ions, generated in the body. In normal circumstances, the concentration of bicarbonate and carbonic acid determines the pH of blood. Further, the bicarbonate buffer system serves as an index to understand the disturbances in the acid-base balance of the body.

2. **Phosphate buffer system** : Sodium dihydrogen phosphate and disodium hydrogen phosphate ($NaH_2PO_4 - Na_2HPO_4$) constitute the phosphate buffer. It is mostly an intracellular buffer and is of less importance in plasma due to its low concentration. With a pK of 6.8 (close to blood pH 7.4), the phosphate buffer would have been more effective, had it been present in high concentration. It is estimated that the ratio of base to acid for phosphate buffer is 4 compared to 20 for bicarbonate buffer.

3. **Protein buffer system** : The plasma proteins and hemoglobin together constitute the protein buffer system of the blood. The buffering capacity of proteins is dependent on the pK of ionizable groups of amino acids. The imidazole group of histidine (pK = 6.7) is the most effective contributor of protein buffers. The plasma proteins account for about 2% of the total buffering capacity of the plasma.

Hemoglobin of RBC is also an important buffer. It mainly buffers the fixed acids, besides being involved in the transport of gases (O_2 and CO_2). More details on hemoglobin are given under respiratory mechanism for pH regulation.

II. Respiratory mechanism for pH regulation

Respiratory system provides a rapid mechanism for the maintenance of acid-base balance. This is achieved by regulating the concentration of carbonic acid (H_2CO_3) in the blood i.e. the denominator in the bicarbonate buffer system. The details of CO_2 transport and the role of hemoglobin in this process are described elsewhere (***Chapter 10, Refer Fig.10.6***).

The large volumes of CO_2 produced by the cellular metabolic activity endanger the acid-base equilibrium of the body. But in normal circumstances, all of this CO_2 is eliminated from the body in the expired air via the lungs, as summarized below.

$$H_2CO_3 \xleftrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O.$$

The rate of respiration (or the rate of removal of CO_2) is controlled by a respiratory centre, located in the medulla of the brain. This centre is highly sensitive to changes in the pH of blood. Any decrease in blood pH causes hyperventilation to blow off CO_2, thereby reducing the H_2CO_3 concentration. Simultaneously, the H^+ ions are eliminated as H_2O.

Respiratory control of blood pH is rapid but only a short term regulatory process, since hyperventilation cannot proceed for long.

Hemoglobin as a buffer : Hemoglobin of erythrocytes is also important in the respiratory regulation of pH. At the tissue level, hemoglobin binds to H^+ ions and helps to transport CO_2 as HCO_3^- with a minimum change in pH (referred to as ***isohydric transport***). In the lungs, as hemoglobin combines with O_2, H^+ ions are removed which combine with HCO_3^- to form H_2CO_3. The latter dissociates to release CO_2 to be exhaled (***Refer Fig.10.6***).

Generation of HCO_3^- by RBC : Due to lack of aerobic metabolic pathways, RBC produce very little CO_2. The plasma CO_2 diffuses into the RBC along the concentration gradient where it combines with water to form H_2CO_3. This reaction is catalysed by ***carbonic anhydrase*** (also called carbonate dehydratase). In the RBC, H_2CO_3 dissociates to produce H^+ and HCO_3^-. The H^+ ions are trapped and buffered by hemoglobin. As the concentration of HCO_3^- increases in the RBC, it diffuses into plasma along with the concentration gradient, in exchange for Cl^- ions, to maintain electrical neutrality. This phenomenon, referred to as ***chloride shift***, helps to generate HCO_3^- (***Fig.21.4***).

MAINTENANCE OF BLOOD pH

The body has developed three lines of defense to regulate the body's acid-base balance and maintain the blood pH (around 7.4).

I. Blood buffers

II. Respiratory mechanism

III. Renal mechanism.

I. Blood buffers

(A buffer may be defined as a solution of a weak acid (HA) and its salt (BA) with a strong base. The buffer resists the change in pH by the addition of acid or alkali and the buffering capacity is dependent on the absolute concentration of salt and acid.) It should be borne in mind that the buffer cannot remove H^+ ions from the body. It temporarily acts as a shock absorbant to reduce the free H^+ ions. The H^+ ions have to be ultimately eliminated by the renal mechanism (described later).

The blood contains 3 buffer systems.

1. Bicarbonate buffer
2. Phosphate buffer
3. Protein buffer.