Acid–base balance: maintenance of plasma pH

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Maintenance of plasma pH ($-\log_{10}[H^+]$) within the range 7.38–7.42 is an essential requirement for life, because many metabolic processes (e.g. enzymatic reactions) are exquisitely sensitive to changes in H^+ concentration. The range compatible with life is 7.00–7.70 (i.e. a 5-fold change in H^+ concentration). The intracellular H^+ concentration is higher (about pH 7.00) than that in extracellular fluid (ECF), but is sensitive to changes in extracellular H^+ concentration. ECF is normally alkaline. This narrow pH range must be maintained in the face of the production of large quantities of volatile acid from cellular metabolism (mainly CO_2) and non-volatile acid from the metabolism of fats and certain proteins. The main problem encountered in the homeostatic control of plasma pH is the defence of the alkaline environment in the face of this massive, daily acid load.

Volatile acid: in terms of the total acid production, CO_2 provides the largest contribution at 15–20 mol/day. This can occur either by hydration of CO_2 to form the weak, volatile carbonic acid (equation 1) or by hydroxylation of CO_2 following the splitting of water (equation 2). The products of both reactions are H^+ and HCO_3^-.

$$CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^- \quad (1)$$

$$H_2O = OH^- + H^+$$

$$OH^- + CO_2 = HCO_3^- \quad (2)$$

Production of this amount of acid would certainly change the plasma pH if it were not for the fact that most of the CO_2 is excreted from the lungs.

Non-volatile acids contribute much less to daily acid production. Such acids include sulphuric acid from sulphur-containing amino acids (e.g. cysteine, methionine), hydrochloric acid from cationic amino acids (e.g. lysine, arginine) and phosphoric acid from the metabolism of phospholipids and phosphorylated amino acids (e.g. phosphoserine). In addition, faecal loss of HCO_3^- from gastrointestinal secretions can be regarded as a significant (and variable) contribution to non-volatile acid production. Metabolism of anionic amino acids (e.g. aspartic, glutamic) and some organic anions (e.g. citrate) yield HCO_3^-, which will partially offset some of the non-volatile acid production. The contribution of non-volatile acids to total acid production depends on dietary composition. If meat is a major component of the diet, non-volatile acids are significant (about 50 mmol/day), whereas this value is lower if the major components are vegetables and fruit.

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Buffer systems in body fluids

A buffer system consists of an undissociated weak acid (HA) and its base (A^-), and can be represented by:

$$HA = H^+ + A^- \quad (3)$$

Following the addition of a strong acid, some of the H^+ is mopped up through the formation of more HA and thus the change in free H^+ is limited. Conversely, the decrease in H^+ caused by the addition of strong alkali is limited by freeing H^+ from the weak acid. The main buffer systems in body fluids are given in Figure 1. The main buffer system in plasma is bicarbonate/carbonic acid, therefore pH can be represented using the Henderson–Hasselbalch equation:

$$pH = pK' + \log_{10}\frac{\text{buffer salt}}{\text{weak acid}} = \log_{10}\frac{[HCO_3^-]}{[H_2CO_3]} \quad (4)$$

where pK' is the apparent dissociation constant.

Since there is little H_2CO_3, the acid moiety of the system is primarily CO_2 which is proportional to the partial pressure of CO_2 (pCO_2 mm Hg). Thus:

$$pH = 6.1 + \log_{10}\frac{[HCO_3^-]}{0.03 \times pCO_2} \quad (5)$$

where 0.03 is the solubility coefficient of CO_2 in plasma

$$= 6.1 + \log_{10}\frac{24 \text{ mmol/litre}}{(0.03 \times 40 \text{ mm Hg}) \text{ mmol/litre}} = 7.4$$

Defence mechanisms

Defence of the alkaline environment is achieved through the operation of three basic mechanisms.

- Physicochemical buffering (i.e. removal of the H^+ by the various reactions listed in Figure 1) is instantaneous but only limits the fall in pH.
- Respiratory compensation is rapid (in minutes) and operates via the control of plasma pCO_2 through changes in alveolar ventilation and subsequent evolution of CO_2; plasma pH is returned towards the normal values, but acid–base status cannot be corrected completely.
- Renal compensation is slower (measured in hours or days) and operates via the control of plasma bicarbonate through changes in the renal secretion of H^+, reabsorption and production of bicarbonate; acid–base status can be corrected.

Disturbances in acid–base balance

It is evident from equations 4 and 5 that disturbances in acid–base balance can occur via changes in either the numerator (plasma HCO_3^- concentration) or the denominator (plasma pCO_2). Respiratory disturbance occurs if the primary change is altered pCO_2 whereas

Main buffer systems in body fluids

Blood					
• Plasma proteins	HPr	=	Pr^-	+	H^+
• Haemoglobin	HHb	=	Hb	+	H^+
• Bicarbonate	H_2CO_3	=	HCO_3^-	+	H^+
Interstitial fluid					
• Bicarbonate	H_2CO_3	=	HCO_3^-	+	H^+
Intracellular fluid					
• Proteins	HPr	=	Pr	+	H^+
• Phosphate	H_2PO_4	=	HPO_4	+	H^+

1

metabolic (non-respiratory) disturbance occurs if the primary change is altered plasma HCO_3^-. Thus, if pCO_2 is either increased (e.g. asphyxia, chronic pulmonary disease, hypoventilation such as following opiate administration) or decreased (e.g. anxiety attacks, rapid ascent to high altitude, voluntary hyperventilation), these disturbances are referred to as respiratory acidosis and respiratory alkalosis, respectively. If plasma HCO_3^- is decreased by addition of non-volatile acids (e.g. uncontrolled diabetes mellitus, renal failure, severe diarrhoea, ammonium chloride ingestion) or increased (e.g. excessive vomiting, sodium bicarbonate ingestion for chronic dyspepsia), these disturbances are referred to as metabolic acidosis and metabolic alkalosis, respectively.

Compensatory responses to these changes can also be predicted from equations 4 and 5. Thus, increasing or decreasing pCO_2 can be compensated for by decreasing or increasing plasma HCO_3^-, whereas acid-induced changes in plasma HCO_3^- can be compensated for by opposite changes in pCO_2. In other words, primary respiratory disturbances are compensated for by metabolic responses, and primary metabolic disturbances by respiratory responses.

Respiratory acidosis

Increasing pCO_2 leads to a reduction in pH (i.e. the equilibrium in equation 1 is shifted to the right with an increase in H^+ concentration). The plasma bicarbonate buffer system cannot be used to compensate for this change because to do so would need the equilibrium simultaneously moving to the left (i.e. in a direction opposite to that which is causing the change). However, some H^+ will be taken up by non-bicarbonate buffers (plasma proteins and phosphates) with a subsequent small elevation in plasma HCO_3^-. CO_2 readily diffuses across all cell membranes, including capillary and RBC membranes. Thus, interstitial fluid H^+ increases and thereby lowers pH to a large extent because the concentration of non-bicarbonate buffers is low. However, the haemoglobin buffer system makes a significant contribution. Thus, the increasing intracellular CO_2 is hydrated or hydroxylated in the presence of the catalytic enzyme, carbonic anhydrase, with the end-products being H^+ and HCO_3^-. The former is buffered by the haemoglobin system and the latter is exchanged for Cl^- across the cell membrane (known as the chloride shift). Thus, the first line of defence (physicochemical buffering) limits but does not restore plasma pH.

It is evident that the second line of defence, respiratory compensation, does not contribute since the primary cause of the change in pH is respiratory.

The third line of defence, renal compensation, is important; H^+ is excreted and plasma HCO_3^- is increased by the renal tubular cells reclaiming virtually all the filtered HCO_3^- and producing HCO_3^-. As stated above, it can take days to compensate fully for the increase in CO_2. Hence, primary respiratory disturbances are followed by a few days of lowered plasma pH before compensation occurs.

Respiratory alkalosis

Decreasing pCO_2 lowers the denominator of equation 4, and the pH becomes more alkaline. Again, the plasma bicarbonate buffer system cannot contribute H^+ since this would require a simultaneous shift in the equilibrium (equation 1) to the right. Non-bicarbonate buffers contribute by releasing H^+ and produce a small reduction in plasma HCO_3^- which restricts, but does not prevent, the rise in pH. Respiratory compensation cannot contribute because the primary disturbance is respiratory. Renal compensation is important in lowering plasma HCO_3^-, by reducing HCO_3^- re-absorption and production by the renal tubular cells.

Metabolic acidosis

Increased production or addition of non-volatile acid to plasma lowers pH. However, the change in pH is limited by both HCO_3^- and the non-bicarbonate buffer systems:

$$H_2SO_4 + 2NaHCO_3 = Na_2SO_4 + 2H_2CO_3 \quad (6)$$
$$2H_2CO_3 = 2H_2O + 2CO_2$$

Thus, the added H^+ is buffered so the concentrations of Hb^-, negatively charged plasma proteins and HCO_3^- are reduced. The H_2CO_3 so formed dissociates into CO_2 and H_2O; the CO_2 is rapidly excreted by alveolar ventilation. In addition, the increase in plasma H^+ stimulates alveolar ventilation so that a further reduction in pCO_2 occurs. Although these compensatory changes minimize any change in pH, full compensation to return acid–base status to normal requires renal excretion of H^+, and tubular reabsorption and production of HCO_3^-.

Metabolic alkalosis

Following the addition of $NaHCO_3$, or the removal of H^+ through excessive vomiting, the sequence of change is the reverse of that described for the addition of acid. Non-bicarbonate buffers contribute, as do alveolar hypoventilation, to minimize the change in pH. Renal compensation occurs through the excretion of HCO_3^-.

Role of the kidneys in regulation of plasma pH

The involvement of the kidneys in acid–base balance is primarily through the reabsorption of filtered HCO_3^- and the excretion of H^+ leading to production of HCO_3^- to replenish buffer stores depleted during buffering of non-volatile acids (i.e. the reverse of the reaction represented in equation 6).

Reabsorption of filtered HCO_3^-: daily filtered HCO_3^- (calculated as glomerular filtration rate × plasma HCO_3^- concentration) approximates 4–5 moles. Renal reabsorption of this ion is in excess of 99.9% of the filtered load. If this high percentage reabsorption did not occur, bicarbonate stores in the body would soon be depleted.

In terms of the contributions of the different nephron segments, 70–85% of the filtered load is reabsorbed in the early part of the proximal tubule. The contributions of the loop of Henle, distal tubule and collecting duct are 15–20%, 3–5% and 1–2% of the filtered load, respectively.

The mechanisms for the reclamation of the filtered HCO_3^- are shown in Figure 2. Intracellular H^+, formed from the splitting of H_2O, is secreted into the tubular lumen by either passive Na^+/H^+ exchange using a protein carrier, or active transport via the energy-requiring proton pump (H^+-ATPase). A third mechanism (H^+/K^+-ATPase) operates in the α intercalated cells in the collecting duct but, quantitatively, this is far less important than the other two mechanisms.

Secreted H^+ combines with filtered HCO_3^- in the tubular lumen to form H_2CO_3 which dissociates to CO_2 and H_2O. The presence of carbonic anhydrase in the luminal cell membrane (proximal tubule and thick ascending limb of the loop of Henle) ensures that this dissociation occurs rapidly. The CO_2 formed diffuses into the cell where it is hydroxylated by OH^- (catalysed by carbonic anhydrase) to form HCO_3^-, which moves across the basolateral cell membrane into the peritubular environment on either Na^+-HCO_3^- co-transporters or Cl^--HCO_3^- ion exchangers.

The rate of HCO_3^- reabsorption appears to be influenced by a number of factors including the amount filtered, ECF volume and arterial pCO_2. Thus, if the amount filtered is increased by increasing the filtered load, total reabsorption is increased. Following ECF volume expansion, reabsorption is reduced. The mechanisms by which these changes occur are uncertain, but the fact that Na^+ reabsorption is similarly affected suggests that HCO_3^- and Na^+ might be linked. The influence of arterial pCO_2 on HCO_3^- reabsorption is thought to be by changes in the filtered load and by a direct effect on the active pumps for H^+ secretion.

Production of HCO_3^-: the secretion of H^+ as described above does not lead to net excretion because the CO_2 formed within the tubular lumen is returned to the cell where more H^+ is formed and then secreted. However, H^+ can be excreted either as neutral ammonium salts (e.g. $(NH_4)_2SO_4$) or as acid buffer salts (NaH_2PO_4). The latter is also referred to in some texts as the excretion of titratable acid. Both these routes for H^+ excretion lead to the formation of one new HCO_3^- for every H^+ secreted.

Excretion of NaH_2PO_4: the mechanisms involved in the formation and excretion of NaH_2PO_4 are shown in Figure 3. H^+ secreted into the lumen, combines with the filtered neutral buffer salt (NaH_2PO_4) to form the acid buffer salt. Intracellular splitting of water to form the H^+ for secretion provides OH^-, which combines with CO_2 to form HCO_3^-, which moves into the peritubular environment with Na^+ released from the neutral salt. Formation of HCO_3^- by this mechanism occurs in the proximal tubule, distal tubule and collecting duct. Note that unlike the reclamation of filtered HCO_3^- (Figure 2), HCO_3^- is newly formed and thus replenishes some of the HCO_3^- utilized in buffering non-volatile acid (equation 6).

The rate of excretion of titratable acid is influenced by the availability of the urinary buffers, the pK of these buffers and tubular fluid pH. The minimal tubular fluid pH is about 4.4. This

Clinical significance

Metabolic acidosis
Increased production of non-volatile acid (uncontrolled diabetes mellitus), excessive loss of HCO_3^- (diarrhoea) and impaired urinary acidification (renal tubular acidosis, renal failure) are compensated by pH-stimulated changes in alveolar ventilation (reduced pCO_2) and increased renal H^+ secretion, which limits HCO_3^- excretion and increases HCO_3^- generation through excretion of titratable acid and NH_4^+ salts. Diarrhoea-induced reduction in extracellular fluid volume (ECFV) enhances H^+ secretion by increasing Na^+ reabsorption at both proximal and distal tubules. In renal failure the contribution of H^+ secretion depends on the extent of the tubular defect; if loss of functioning tissue is severe, HCO_3^- is administered.

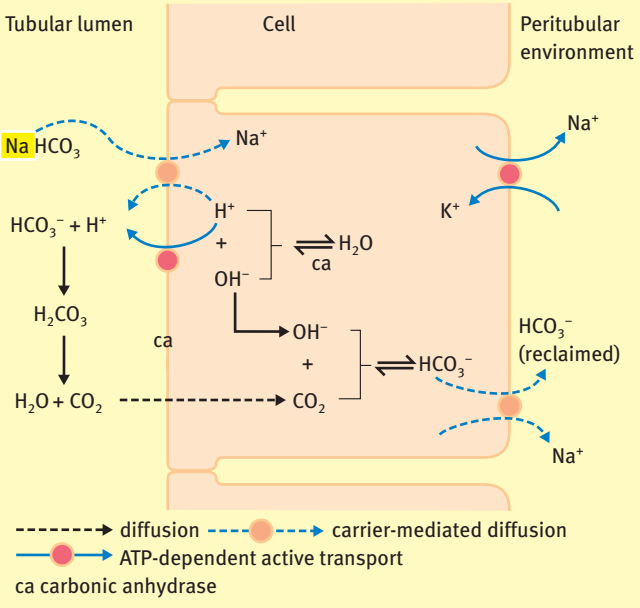
Metabolic alkalosis
Compensation for increased plasma HCO_3^- (excessive ingestion of $NaHCO_3$) or excessive loss of non-volatile acid (vomiting) occurs by reductions in alveolar ventilation (increased pCO_2) and H^+ secretion hence an increase in HCO_3^- excretion. If vomiting causes significant ECFV depletion, Na^+ reabsorption (hence H^+ secretion) increases thereby exacerbating the alkalosis. Repletion of ECFV minimizes H^+ secretion and increases HCO_3^- excretion.

Respiratory acidosis
Acute (depression of ventilation by barbiturate overdose) and chronic (chronic pulmonary disease) increases in pCO_2 are compensated by a rise in plasma HCO_3^- due in part to physicochemical buffering but primarily to increased renal H^+ secretion.

Respiratory alkalosis
Compensation for acute reductions in pCO_2 (drug-induced increase in ventilation, anxiety) is by physicochemical buffering and reduced H^+ secretion, both of which decrease plasma HCO_3^-.

Compensatory mechanisms for metabolic and respiratory disturbances minimize changes in pH but complete correction of acid–base disturbances requires removal of the primary disturbance.

Mechanisms of HCO_3^- reabsorption



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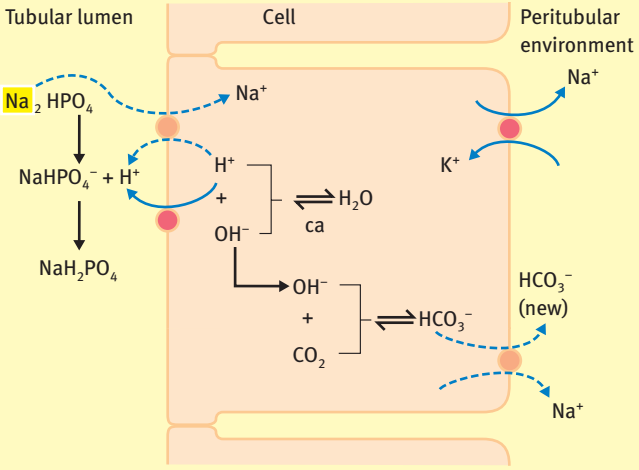
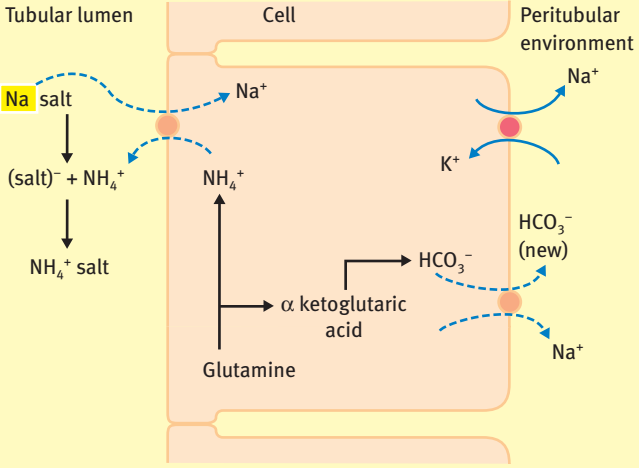
Mechanisms of H^+ secretion and replenishment of HCO_3^- buffer stores

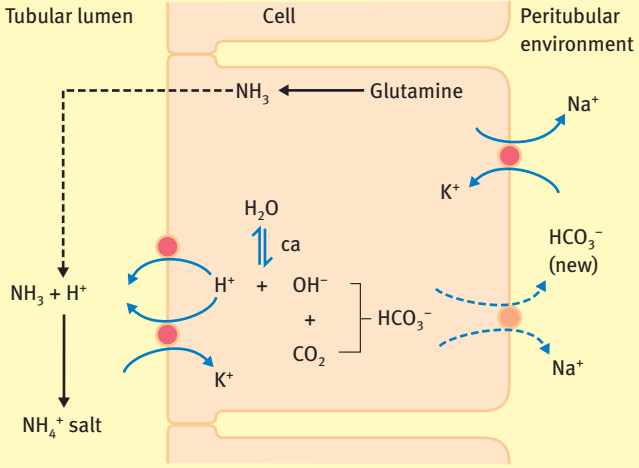
Excretion of acid buffer salt



Secretion of NH_4^+ and formation of NH_4^+ salt



Secretion of NH_3 and formation of NH_4^+ salt



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probably represents the maximum gradient against which H^+ ions can be secreted. At this pH, it is likely that the buffering capacity afforded by the neutral phosphate buffers (pK = 6.8) will have been exceeded; in other words, all the phosphate will be in the acid form (NaH_2PO_4). Under these conditions, increases in H^+ excretion would occur by increasing plasma PO_4^- concentration (thus filtered load) or if other urinary buffers were available. Creatinine is such a buffer (pK about 5), but it is present only in low concentrations and, therefore, does not make a significant contribution.

Clearly, if these were the only mechanisms available for H^+ ion excretion, urinary pH would soon decrease to the minimal value (i.e. there would be little further net secretion of H^+ and both extracellular and intracellular acidosis would occur) with the pH decreasing well below the range compatible with life.

Excretion of ammonium buffer salts: the mechanisms involved in the formation and excretion of NH_4^+ salts are shown in Figure 3. H^+ produced within the cell combines with NH_3 to form NH_4^+. This occurs either within the cell as in the proximal tubule, or in the collecting duct lumen.

In the proximal tubule, NH_3 is derived from deamination of glutamine and NH_4^+ gains access into the tubular lumen by replacing H^+ on the Na^+/H^+ exchanger in the apical membrane. This NH_4^+ can be reabsorbed from the thick ascending limb of the loop of Henle, perhaps by replacing K^+ on the triple transporter ($Na^+/K^+/2Cl^-$) in the apical membrane. Since water is not reabsorbed in the thick ascending limb of the loop of Henle, NH_4^+ reabsorption contributes to the single osmotic effect which is multiplied by countercurrent multiplication. A steep cortico-papillary concentration gradient for NH_4^+ is produced with the highest value in papillary interstitial fluid. As with all buffer systems, the NH_4^+/NH_3 system exists as two moieties, so the concentration of NH_3 increases with NH_4^+ concentration. This high concentration promotes NH_3 diffusion into the collecting duct lumen where it combines with secreted H^+ to form the impenetrable NH_4^+ – a process known as diffusion trapping or non-ionic diffusion. In the α intercalated cells of the collecting duct, H^+ is secreted either by H^+-ATPase or the active H^+/K^+ exchanger, both of which are found in the apical membrane. Rapid removal of NH_3 as NH_4^+ maintains the favourable gradient for NH_3 diffusion, thereby enabling removal of secreted H^+. As with the excretion of titratable acid, Figure 3 shows that secretion of both NH_4^+ in the proximal tubule and H^+ in the collecting duct results in the production of HCO_3^- which moves, with reabsorbed Na^+, into the peritubular environment (i.e. H^+ excretion leads to replenishment of the HCO_3^- buffer stores depleted by addition of non-volatile acids).

The rate of NH_4^+ excretion appears to be influenced by urinary pH, and the severity and duration of the acidosis. The first appears to modify NH_3 secretion and the second to be related to the quantity of intracellular NH_4^+ produced in the proximal tubules. ◆

FURTHER READING

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