ACID-BASE PRINCIPLES

Blood plasma pH

Acids when dissolved in water yield protons (H^+); bases consume or bind protons. Acidity measures the concentration of free H^+ in a solution. The H^+ concentrations in aqueous solutions are in nanoequivalents per liter (10-9 Eq/L). In water there is 100 nEq/L H+ (and OH^-). This equals 10-7 Eq/L, or, in a negative log scale, the pH scale, pH = 7. The pH = log $1/[H^+]$. Thus pH is inversely related to $[H^+]$. Blood plasma has pH=7.4 or $[H^+]$ = 40 nEq/L, which is somewhat alkaline. This pH is kept in a narrow range (7.40 +/- 0.02) in spite of continuous ingestion and metabolic production of acids.

Sources of Acid

Acid production is derived from metabolism of sulfur containing (70 mEq/day), cationic amino acids (140 mEq/day), and substances containing acid phosphates (H_2PO4-, 30 mEq/day). Normally, this is balanced by H^+ consumption in metabolism of anionic amino acids (110 mEq/day) and other organic anions (60 mEq/day), and by urinary excretion of ammonium (40 mEq/day) and acid phosphate (30 mEq/day) .

Buffering

Buffering occurs when pH changes are minimized. It involves chemical and physiological processes.

Chemical (in the ECF) and **respiratory buffering** are almost immediate. ICF buffering involves transfer of H^+ in or out of the ICF. Intracellular chemical buffering may be fast if it involves organic acid or slower (an intermediate step) for poorly cell permeable inorganic acids such as HCl or H_2SO_4. Long term regulation occurs through kidney urinary excretion of H^+, with resulting reabsorption and generation of base (HCO_3^-).

Chemical buffering is due to conversion of a strong acid (such as HCl) into a weak acid (such as H_2CO_3 or H_2NaPO_4) through chemical reaction with a weak buffer base (such as $NaHCO_3$ or HNa_2PO_4). The higher the weak base concentration, the better the buffering. The weaker the resulting acid, the better the buffering.

The weakness or strength of an acid depends on its dissociation constant (Kd). A weak acid when dissolved yields few protons and its Kd is small. A strong acid when dissolved dissociates completely and yields many protons; its Kd is large. The pK is the negative log of the Kd, it is inversely related to the Kd: pK= log (1/Kd). Weak acids have high pK. Strong acids have low pK.

Titration of a buffer

When an acid HA dissociates into H^+ and buffer base (A^-), the mass action equilibrium is :

$[H^+] \times [A^-] = [HA] \times Kd$ so that $[H^+] = Kd \times ([HA]/[A^-])$

When [HA] = [A-], then [H+] = Kd.

On a log scale, pH = pK + log ([HA]/[A-]) and when [HA] = [A-], log [A-]/[HA]=log 1 = 0, so pH = pK.

When the pH of a buffered solution is more alkaline (higher) than the buffer pK by 1 unit, the log [A-]/[HA] = 1and the ratio [A-]/[HA] = 10. The proportion of the total buffer (HA + A-) in the dissociated weak base form (A-) will be 10/(10+1) = 0.91 (91%). When, by adding strong acid the solution, the pH becomes more acid than the buffer pK by one unit, the log [A-]/[HA] = -1and the ratio [A-]/[HA] = 1/10. The proportion of the total buffer (HA + A-) in the dissociated weak base form (A-) will be 1/(10+1) = 0.091 (9.1%). So within +1 and -1 units of the buffer pK, 91-9.1 = 82% (most) of the buffer reacts (is titrated) with H+ and is converted from A- to HA. Beyond this pK region, there is little buffering of the pH on adding acid to the buffer containing solution. Thus, buffering is only effective within the pK region of the buffer (+/- 1 pH unit).

Isohydric principle. When a solution (or compartment) contains more than one buffer, all buffer pairs (HA and A-) in the system are in equilibrium with the same proton concentration: Only those buffers with a pK within 1 pH unit of that in the solution participate effectively in the buffering of the solution pH.

Buffering power or capacity depends on the buffer concentrations and on the pK of the buffers present in that compartment.

Body buffers

The most abundant buffers in the body fluids are 1) bicarbonate/CO_2 in the ECF (400 mEq), 2) bicarbonate in the ICF and bone (another 400 mEq), 3) histidine groups of intracellular proteins (about 400 mEq), and 4) small amounts of intra and extracellular phosphates (40 mEq). These buffers (total about 1250 mEq) maintain the ECF and ICF pH within 0.3-0.4 pH units of their normal values as long as their capacity to bind protons (about 20 mEq/Kg body weight) is not exceeded.

Bicarbonate/$C0_2$ System

Buffering by bicarbonate/$C0_2$ comprises hydration of dissolved $C0_2$ ($[C0_2]d$) and dissociation of carbonic acid:

$$(C0_2)d + H_20 <=> H_2C0_3 <=> H^+ + HC0_3^-$$

The mass action equilibrium for the dissociation is: (1) $Kd = [H^+] \times [HCO_3^-] / [H_2C0_3]$

The equilibrium of the simultaneous hydration is: (2) $Kh = [H_2C0_3]/([C0_2d] \times [H_20])$

From (2) $Kh \times [H_20] = K1$ (constant) and $K1 = [H_2CO_3]/[CO_2d]$

and (3) $[H_2CO_3] = K1 \times [CO_2]d$

from Henry's Law (4) $[CO_2]d = a \times PCO_2$ a is the CO_2 solubility coefficient.

Thus (5) $Kd = [H^+] \times [HC0_3^-] / K1 \times a \times PCO_2$

Solving for [H+] (6) $[H^+]=KdK1\ a\ PCO_2/[HCO_3^-]$

Since KdK1a = 24 (7) $[H^+]$(in nM)= 24 PCO_2(in mmHg) / HCO_3^- (in mM) (Henderson's equation)

Taking the negative log on both sides

(8) **$-\log [H^+]=-\log KdK1+\log[HC0_3]/aPC0_2$**

Calling -log KdK1 = pKe (effective pK)

(9) $pH = pKe + \log [HCO_3^-]/aPCO_2$ (Henderson-Hasselbalch equation)

where

pKe = 6.1; a = 0.0301; $[HCO_3^-]$ in mM; PCO_2 in torr (or mmHg).

Buffering by the $HC0_3^-/CO_2$ system

In spite of its pKe = 6.1 the HCO_3^-/CO_2 system functions as an effective buffer in maintaining the normal arterial blood plasma pH at 7.4 because one of its component is volatile and the system is open. Consider the following example:

The ECF contains 24 mM NaHCO3 and is equilibrated with 5.6% gaseous CO_2. At 37C and PB = 760 torr,

$PCO_2 = 0.056 \times (760-47) = 40$ torr, $aPCO_2 = .0301 \times 40 = 1.2$ mM and $[HCO_3-]/ aPCO_2 = 24/1.2 = 20/1$;

Log $[HCO_3-]/aPCO_2$ = Log 20/1 = 1.3; pH = 6.1 + 1.3 = 7.4 or [H+]= 24 x 40/24 = 40 nM

Buffering of strong acid in a closed system. If we had 1 L of such a bicarbonate-CO2 solution in a closed container and added enough strong acid (e.g. 12 mmoles HCl) to decrease the

[HCO3-] to about half (to 12 mM) by the reaction HCl + NaHCO3 <=> H2CO3 + NaCl, then twelve mmoles of H2C03 (really of H2C03+C02d) will be now present. Thus

[HC03]= 12; aPCO2 = 12; PCO2 =12/0.03= 400 torr and [HCO3-]/aPCO2 = 1.0 ; log 1 = 0; pH = 6.1 + 0 = 6.1 and

[H+]= 24x400/12 =800 nM; which represents a severe acidosis.

Buffering of strong acid in an open system. Suppose the container with NaHC03 solution is open to the atmosphere and we bubble continuously 5.6% C02 to maintain the PCO2 at 40 torr. Addition of 12 mmoles of HCl will reduce [HC03-] to 12 mM but the generated H2C03 will escape to the atmosphere by conversion to gaseous CO2 because the PCO2 is maintained at 40 torr.

[HC03] = 12 mM; aPC02 = 1.2 mM; [HCO3-]/aPCO2= 10; log 10 = 1; pH = 6.1 + 1 = 7.1; [H+] = 24 x 40/12 = 80 nM

Conclusion: The resulting pH change is much smaller in an open system than in a closed system. For a buffer pair in which the weak acid is volatile, buffering of the pH upon addition of protons to an open system is very effective. In addition for such a buffer system the effective buffering range is wider (>1 pH unit above their pK) than for non volatile buffers or than for closed systems.

Buffering of strong acid in an open and regulated system. Alveolar ventilation (VA) is under neural control. Increases in VA in response to reduced pHa lead to increased pulmonary excretion of C02 and lowering of the PaC02 . We can simulate this response by additional bubbling of air through the solution (simulating hyperventilation); the PC02 will be lower than normal (e.g. 20 torr), so

[HCO3-] = 12; aPCO2 = 0.03 x 20 = 0.6; [HCO3-]/aPCO2 = 20; log 20 = 1.3; pH = 6.1+1.3 = 7.4; [H+]=24 x 20/12 = 40nM

Thus, in an open system with perfect "physiological" control, the pH change due to addition of strong acid is completely blunted. In real life, for each 1 mM decrease in [HCO3-] due to acid loading, the PaCO2 should fall by about 1 torr if the respiratory centers respond normally to the low pHa. Usually the compensation is not perfect, some acidosis persists, and is limited by loss of bicarbonate in the urine due to the low PaCO2 (see later).

Base Excess and Base Deficit

Titration of body fluids with CO2. When the PCO2 of a pure NaHCO3 solution is elevated, the pH will decrease with little change in the [HCO3]. Upon increasing the PCO2, both the [CO2]d and the [H2C03] will increase and some of the H2C03 will dissociate into H+ (responsible for the decrease in pH) and HC03-, the increase [HC03-], as that in [H+], is in the nanomolar (10-

9M) range. When the PCO2 of blood is similarly raised, the decrease in pH will be smaller (since blood contains buffers) and the increase in [HCO3-] will be larger than observed in a pure NaHC03 solution.This buffering of CO2 is due to the presence of non-bicarbonate buffers in blood and tissues (mostly Hb, other proteins, and phosphates). Non-bicarbonate buffers associate with H+ derived from H2C03, promote formation of H2C03 (by hydration of C02) and dissociation of H2C03 into H+ ions (which are buffered by these substances) and more HC03-, which increases in concentration.

The changes in pH and [HC03] in arterial blood in vivo upon chronic exposure to changes in PaC02 (chronic hypoventilation or C02 inhalation or chronic hyperventilation) differ from those in the acute situation. Chronic exposure to a high PaC02 results in much smaller changes in pHa and much larger increases in plasma [HC03-] than on acute exposure to the same PaC02. This higher chronic buffering capacity for C02 is due to the kidneys' generation of HC03-, whose ECF concentration increases and minimizes the drop in pH due to increased PC02. Such "chronic" buffering of C02 is 10 times larger than the acute buffering by non-bicarbonate buffers

The base excess (BE) or base deficit (negative BE) is calculated from the change in [HCO3-] that persists in the system when the pH is brought back (by acutely changing the PCO2) to the standard value of 7.4. At that pH, all non-bicarbonate ECF buffers (proteins, phosphates, etc.) have the same ratio of dissociated to undissociated buffer forms as existed before addition of acid or base. The base (positive values) or acid (negative values) excess is thus reflected only by the change in Standard Bicarbonate, [HCO3-]St ,and is calculated as follows:

BE = Change in [HC03-]St = ([HCO3-]x - 24) + BC x (pHx-7.4)

[HCO3-]x and pHx are the values measured in a blood sample and BC is the buffer capacity. As discussed above, the value of BC is not constant but depends on the elapsed time. In chronic acidosis the value of BC is very large (100 slykes) while BC = 10slykes in acute acidosis. Unfortunately the ICF is not in chemical equilibrium with the ECF and we can only give an educated guess of what is happening intracellularly. At the different stages, the product of the apparent volume of distribution of bicarbonate (40% of body weight in acute acidosis, 80% of body weight in chronic conditions) times the base deficit yield estimates of the amount (mEq) of bicarbonate to be replaced (or if in excess, to be removed). The initial target should be to bring the pH to a safe range (7.25-7.55, [H+], 28-56 nM), rather than to completely correct the disturbance.

RENAL REGULATION OF BICARBONATE

The kidneys regulate the [HC03-] by

1) conserving or excreting the HC03- present in the glomerular ultrafiltrate;

2) producing new HCO3- which enters the body fluids as the kidneys excrete ammonium salts and titratable acids (this sum is called net acid) in the urine

Renal Conservation of HCO3-

If urine pH < 6, the concentration of HC03- in the urine is very low (e.g.< 0.1 mEq/L). The glomerular ultrafiltrate has 24 mM. Thus, most HC03- filtered (4500 mEq/day) is reabsorbed, mostly (90%) along the proximal tubules.

Proximal tubule reabsorption of bicarbonate

Reabsorption: H+ secretion from cells across the luminal membrane is mostly in exchange for Na+ ions, and to a small extent ,through a proton ATPase. Secreted H+ react with filtered HC03- to form H2CO3. In the presence of carbonic anhydrase (type IV), luminal H2CO3 rapidly dehydrates to CO2 + H20. Drugs that inhibit carbonic anhydrase (e.g., acetazolamide) interfere with proximal reabsorption of NaHCO3 and induce a bicarbonate (osmotic) diuresis. Inside the cell, dissociation of H2O into OH- and H+ is promoted by hydroxylation of CO2 (OH- + CO2 => HCO3-) to generate bicarbonate, catalyzed by soluble (type II) carbonic anhydrase. H+ is exchanged for Na+ ions through a high capacity isoform (NHE3) of the Na-H exchange proteins. Bicarbonate exits the cell through the basolateral membrane in a 3:1 cotransport with Na+. The net result is that NaHC03 disappears from the lumen and appears in the blood-side of the proximal tubule cells.

Regulation: Proximal reabsorption HCO3- is stimulated by (1) decreases in cell pH (due to metabolic acidosis, respiratory acidosis or to decreases in cell K). Low cell pH acutely activates Na-H exchange and chronically induces expression of NHE3 and Na-3HCO3 cotransporters and (2) high levels of Angiotensin II stimulate Na-H exchange (e.g., contraction of the extracellular fluid).

HC03 reabsorption in the collecting ducts

Reabsorption

(1) The amount of HCO3- reabsorbed are much smaller than in the PT.

(2) Reabsorption can be easily saturated by increases in HCO3- load (low Vmax).

(3) Can occur with larger transepithelial pH difference (4.5 -7.4) than in the proximal tubules (6.8 -7.4)

(4) Most is not mediated by luminal carbonic anhydrase.

(5) H+ secretion is mostly by luminal proton (and some by proton-K+) ATPases of alpha-intercalated cells

(6) Basolateral transport of HCO3- is via Cl- exchangers.

(7) Beta-intercalated cells secrete bicarbonate into the lumen and extrude H+ into the ECF.

Regulation: HC03 reabsorption in the CD is stimulated by the following:

(1) High concentration of H+ inside activate the H+ pumps in the cells (as in acidosis or K+ deficiency);

(2) In respiratory or metabolic acidosis, more proton pumps are inserted into the luminal membranes of alpha-intercalated cells.

(3) Low [H+] (i.e. at more alkaline pH) in the tubular fluid.

(4) Increase in the negativity of the tubular lumen (when Na+ reabsorption by principal cells is increased by aldosterone or when the load of slowly reabsorbed PO4-, SO4- or HCO3- increase).

(5) Aldosterone acts directly to increase H+ secreting pumps in alpha-intercalated cells.

Renal Production of HC03

The kidneys can generate (produce) new HC03- through (a) urinary excretion of ammonium (NH4+) salts and (b) urinary excretion of titratable acids.

NH4+ excretion

Renal production of ammonium. Glutamine enters proximal tubule cells from the peritubular capillary blood and from the filtrate. Within the cell, glutamine enters the mitochondria and is deamidated (by glutaminase I enzyme) and deaminated (by glutamic dehydrogenase). There result two molecules of NH4+ and one of divalent alpha-ketoglutarate anion. This anion is oxidized to 2 HCO3- + 4 C02 + H20. NH4+ is secreted into the lumen through the Na+-H+ (or NH4+) exchanger. Bicarbonate exits through basolateral cotransport with Na+. For each NH4+ excreted, one bicarbonate enters the ECF.

Excretion. Ammonium produced and secreted in cortical proximal tubules is transferred to the renal medullary interstitium and from there to the collecting ducts and into the urine. The TAL reabsorbs NH4+ via a luminal NH4+ - Na+ 2Cl- cotransporter, where it replaces some K+. NH4+ dissociates into NH3 (volatile) and H+. The gaseous NH3 diffuses to the medullary interstitium and to the descending limbs where the countercurrent system generates a corticomedullary NH3 (and NH4+) gradient . The NH3 diffuses from the medullary interstitium to the acid fluid in the collecting ducts where it reacts with H+ forming impermeant NH4+ which is excreted in the urine. The more acidic the tubular fluid, the faster and larger the NH3 transfer. Urine NH4+ (mEq/L) may be roughly estimated from the urine cation gap: urine [Na+] + [K+] - [Cl] in mEq/L.

Regulation

In acute acidosis, increases in renal NH4+ excretion are due to rerouting of NH3 from renal venous blood to the urine due to a more acidic urine pH and sometimes, to increases in urine flow. In addition, an acid intracellular pH activates mitochondrial glutamine transport and metabolism (deamidation) and oxidation of the resulting alpha-ketoglutarate.

In chronic metabolic acidosis, there is also induction, through genomic effects on an acid pHi, of basolateral and mitochondrial glutamine transporters, of glutaminase, and other enzymes that participate in the oxidation of glutamine. These adaptations to chronic acidosis allow large amounts of ammonium to be excreted at any urine pH, even at pH 7.

Excretion of titratable acid

The major buffer in urine is phosphate. At pH 7.4 as in the glomerular filtrate, only 20% of the phosphate is in the di-acid phosphate form (H2P04-) and 80% is in the monoacid form (HPO4=). In the proximal tubules, H+ secretion progressively decreases pH (to 6.8) and titrates up to 50% of the phosphate in the lumen to the diprotonated form (H2P04-). Luminal Na+ is reabsorbed in exchange for cell H+ and exits, together with HCO3- formed in the cell, across the basolateral membrane. For every proton secreted that titrates the phosphate in the lumen, there is generation of one molecule of bicarbonate that enters the circulation and helps restore the buffering capacity of the body.

H+ secretion in the collecting ducts, through luminal proton ATPases, can acidify the urinary fluid to pH < 6. At this pH practically all phosphate has been converted to the diprotonated form. Again, one HC03- is generated for each H+ secreted due to titration of the phosphate from the mono- to the di-protonated form. Diprotonated phosphates are excreted. Other buffers such as creatinine and b -hydroxybutyrate contribute little to TA excretion except when urine pH is < 5.

Regulation. The rate of urinary excretion of titratable acid depends on: a) the urine pH and b) the rate of excretion of buffers (phosphate, creatinine and b -hydroxyburyrate). In acidosis, titratable acid excretion is enhanced due mostly to the low urine pH and to a small increase in phosphate excretion (due to reduced reabsorption and loss of bone phosphate). b -hydroxybutyrate can contribute significantly (up to 30%) to the high rates (10 fold increment from 30 to 300 mmol/day) of titratable acid excretion observed in severe ketoacidosis when the urine pH reaches values as low as 4.5.

Quantities. The concentration of titratable acid (mEq/L) in the urine can be quantified by direct measurement or roughly estimated (with large probability of error, when urine pH < 6 and no alcohols are present in the urine) from the urinary osmolar anion gap (urine osmolarity minus the

sum of urine urea (mM), glucose (mM, if present) and 2x Cl-(mEq/L) concentrations) divided by 2.

Net acid excretion. The sum of the NH4+ excretion and the titratable acids excreted (in milliequivalents) minus the bicarbonate (mEq) that might escape in the urine is called NET ACID EXCRETION and equals the milliequivalents of new bicarbonate produced (generated) by the kidneys to restore the buffer reserves of the body fluids.

ACID-BASE IMBALANCE and COMPENSATION

Definitions

When pHa (arterial blood pH) differs from 7.4 +/- 0.02 (or the [H+] differs from 40 +/- 2 nEq/L) there occurs acidemia (pHa < 7.38, [H+] > 42 nEq/L) or alkalemia (pHa > 7.42, [H+] < 38 nEq/L).

If the pHa change is due primarily to a change in PaCO2, there is respiratory acidosis (PaCO2 > 42 mmHg) or respiratory alkalosis (PaCO2 < 38 mmHg).

When the pHa change is due primarily to a change in [HCO3-] from its normal value of 24 mM, there is metabolic acidosis ([HCO3-] < 22 mM) or metabolic alkalosis ([HCO3-] > 26 mM).

Note: -emia refers to changes in blood; acidosis and alkalosis refer to pathophysiologic processes that lead to pH changes in blood

(A) Metabolic acidosis: pH < 7.38; HCO3- < 22 mM; PaCO2 1 mmHg decrease per 1 mM decrease in HCO3- (acute or chronic)

Causes:

Metabolic acidosis is the most frequent acid-base imbalance and may be due to:

(1) Extrarenal loss of bicarbonate, with hyperchloremia and increased urinary excretion of NH4+ (evident as high urinary cation gap: [Cl-] - [Na+] - [K+] >> 0)

(2) Urinary loss of HCO3- (alkaline urine, with high bicarbonate, and little NH4+ and thus no urine cation gap)

(3) Accumulation of organic anions (lactacidosis, ketoacidosis) with large plasma anion gap (due to organic anions, [Na+]+[K+]-[Cl-]-[HCO3-]>>15), abundant urinary NH4+ but no urinary cation gap (NH4+ is excreted with organic anions so that there is a large urinary osmolar gap: Uosm - 2([Na+]+[K+]) - [urea] - [glucose] >>0. Only lactacidosis can develop in minutes (as in shock).

(4) Decreased kidney production of HCO3- (hyperchloremia, no plasma anion gap, and low urinary excretion of ammonium, (urinary cation gap =0); severe chronic renal failure may result

in metabolic acidosis with increased plasma anion gap (due to high plasma [Pi]) and low urinary NH4+ excretion.

Compensations:

(1) Immediate buffering by reaction with ECF HCO3- represents ~40% of rapid (~2 hrs) buffering of acid. HCl + NaHCO3 => NaCl+ H2CO3 + CO2 + H2O

(2) Respiratory compensation. A low pHa stimulates VA, so PaC02 decreases minimizing the decrease in pHa. For each 1 mM decrease in [HCO3-] a 1 mmHg drop in PaC02 is expected.

Note: Because of respiratory compensation for metabolic acidosis, PaCO2 is expected to be below its normal range or (PaCO2 < 38 mmHg). If , because of disease, there is no respiratory compensation, then PaCO2 will be normal or elevated, and the respiratory system is contributing to the acidemia (see Respiratory Acidosis below)..

(3) Tissue phase. Entry of H+ into cells accounts for ~60% of rapid (~2 h) buffering of poorly permeable acids (HCl or H2SO4). This phase is capable of buffering 100% of the acid by 24 h, and is due to the following ion exchanges and buffering of H+ by cell proteins and HCO3-:

(a) Na+ in the ICF for H+ from the ECF; occurs in most tissues including bone; accounts for 65% of the entry of protons into the ICF (and bone).

(b) ICF K+ for ECF H+; accounts for 25% of the entry of H+ into the ICF. May result in hyperkalemia (6-7 mEq/L) that affects muscle and nerve cells and induces cardiac arrythmias.

(c) ECF Cl- for ICF HC03-; accounts for 10% of the ICF buffering of H+; reduces ICF HC03- and intracellular pH; occurs mostly in red cells where Hb buffers excess H+.

(4) Renal phase. Generation of bicarbonate through urinary excretion of ammonium and titratable acids, restores the depleted cell HCO3- and buffer base reserves over 2-3 days. Manifest only in chronic stage.

(B) Metabolic alkalosis: pHa > 7.42; [HCO3-] > 26 mM; PaCO2 0.75 mmHg increase for each 1 mM increase in [HCO3-] (chronic or acute)

Causes:

(1) Loss of gastric juice (vomiting, suction)

(2) Side effect of diuretics and other forms of ECFV contraction.

(3) Hyperaldosteronism of volume depletion promotes renal H+ secretion, generation and retention of HCO3-.

(4) In hypokalemia, K+ shifts out of cells in exchange for H+, inducing extracellular alkalosis and intracellular acidosis.

Compensations:

(1) Respiratory. As pHa increases, VA is depressed and PaCO2 increases (PaCO2 > 42 mmHg). This normalizes blood pH but is limited by ensuing hypoxia. For each 1 mM rise in HCO3- there is expected a 0.75 mmHg rise in PaCO2; if this does not occur, there is a respiratory tendency to alkalosis.

(2) Cell ionic exchanges. Some 25% of the bicarbonate load is neutralized by H+ derived from intracellular buffers that exchange the H+ for extracellular Na+. In addition, ~2% of extracellular HCO3- enters red cells in exchange for Cl-.

(3) Metabolic. Increases in endogenous organic acid production neutralize ~5 % of an acute HCO3- load. High pHa increases production of lactic and citric acids which decrease [HCO3-]. High blood pH stimulates glycolysis and inhibits the citric acid cycle.

(4) Renal excretion of HCO3- rises when its concentration in plasma increases. Lowering of [HCO3-]pl is limited by high renal reabsorption rate stimulated by high PaCO2, by ECF volume contraction, by hyperaldosteronism, by K+ depletion, and by hypochloremia. These tend to perpetuate the high [HCO3-]pl. Beta-intercalated cells in CCD secrete bicarbonate, increasing its urinary excretion.

(C) Respiratory alkalosis: pH > 7.44; PaCO2 < 38 mm Hg; [HCO3-] decreases (<24 mM) by 0.5 mM (chronic) or 0.1 mM (acute) per each 1 mmHg drop in PaC02

Cause: Alveolar hyperventilation (altitude, hysteria, aspirin excess)

Compensations

(1) Cell buffers. In the acute state there is a 0.1 mM decrease in [HCO3-] for each mmHg decrease in PaCO2. This decrease is due to enhanced dissociation of H+ from cell buffers when the [H+]i decreases due to the low PaCO2. Cell H+ exchange for ECF Na+ and K+ and react with the ECF HCO3-, reducing its concentration. Some extracellular HCO3- enters cells in exchange for Cl- and is titrated by H+ dissociating from the cell buffers.

In the chronic state, there is a 0.5 mM decrease in [HCO3-] for each one mmHg decrease in PaCO2. This is due to:

(2) Renal compensation due to increased HCO3- excretion associated with the low PaCO2, which decreases HCO3- reabsorption. Urinary excretion of NH4+ and titratable acid are transiently reduced, leading to accumulation of metabolic and dietary acids which help reduce ECF [HCO3-] ([HCO3-] < 22 mM). Eventually urinary HCO3- excretion ceases and excretion of NH4+ and titratable acid resumes.

(3) Metabolic compensation by increased production of lactic and citric acids that react with and reduce [HCO3-]ecf

(D) Respiratory acidosis: pH < 7.38; PaC02 > 42 mm Hg; [HCO3-] increases (>24 mM) by 0.25 mM (chronic) or 0.05 mM (acute) per each 1 mmHg rise in PaC02

Cause: Alveolar hypoventilation

Compensations:

(1) Fast cell ion exchanges. An acute small rise in [HCO3-]pl is due to exchange of ECF H+ for ICF (or bone) Na+ (37%) or for ICF K+ (13%) and to exchange of ECF Cl- for ICF (red cells) HCO3- (30%). These rapid ionic exchanges are associated with CO2 buffering by intracellular proteins. For each 1 mmHg increment in PaCO2 there is a small acute 0.06 mM increment in HCO3-.

(2) Metabolic. Reduced production of lactic acid contributes about 5% to the acute increase in [HCO3-]pl.

(3) Renal. Increased HCO3- reabsorption stimulated by high PaCO2 prevents urinary loss of bicarbonate.

In the transition to the chronic stage (1-3 days), enhanced renal NH4+, and titratable acid excretion contribute to further increase [HCO3-] in ECF and ICF above normal ([HCO3-] > 26 mM), returning pH towards normal. As the pH stimulus decreases, renal NH4+ and titratable acid excretion subside. Renal reabsorption of bicarbonate remains elevated as long as the PaCO2 is high.