REGULATION OF EXTRACELLULAR FLUID

DEFENSE OF TONICITY:

- This is primarily the function of the vasopressin-secreting and thirst mechanisms
- The total body osmolality is directly proportionate to the total body sodium plus the total body potassium divided by the total body water
    - Changes in the osmolality of the body fluids occur when a disproportion exists between the amount of these electrolytes and the amount of water ingested or lost from the body
    - **Total body osmolarity depends** on:
        - **Na**
        - **K**
        - **Total body water**
- When the effective osmotic pressure of the plasma RISES, VASOPRESSIN SECRETION IS INCREASED
    - Also, thirst mechanism is stimulated
        - As a result, WATER IS RETAINED and thus dilutes the hypertonic plasma and water intake is increased
- CONVERSELY:
    - When the plasma becomes HYPOTONIC, vasopressin secretion is decreased and "solute-free water" is excreted

- Normal plasma osmolality = **285-295mosm/kg of H2O**

- **Calculated osmolarity: 2 Na + Glucose + Urea**

- **Osmolarity** is the number of osmoles of solute in a litre of solution
    - Osmoles per VOLUME
    - Volume changes with temperature so not used in physiology

- **Osmolality** is the number of osmoles of solute in a kilogram of solvent
    - Osmoles per unit of MASS
    - Mass constant with temperature

- If the amount of solute is low, osmolarity and osmolality can be considered the same.

- **Tonicity** is the measure of the osmotic pressure gradient between two solutions.
    - Unlike osmolarity, **tonicity is only influenced by solutes that cannot cross this semipermeable membrane**, because these are the only solutes influencing the osmotic pressure gradient.

- Thus, you can have iso-osmolar solutions which are not isotonic.

DEFENSE OF ECF VOLUME:

- Volume of the ECF is determined primarily by the total amount of osmotically active solute in the ECF
  - **The amount of Na in the ECF is the most important determinant of ECF volume**
    - THEREFORE, the mechanisms, that control Na balance are the major mechanisms defending ECF volume
- **Volume stimuli OVERRIDE the osmotic regulation** of vasopressin secretion
- **VOLUME IS MORE IMPORTANT THAN OSMOLARITY**

- Angiotensin II stimulates:
  - ⇑ aldosterone
  - ⇑ vasopressin
  - ⇑ thirst

- In disease states, loss of water from the body (DEHYDRATION) causes a moderate decrease in ECF volume
  - Loss of Na in the stools (diarrhoea), urine (severe acidosis, adrenal insufficiency) or sweat (heat prostration) decreases ECF volume markedly and eventually LEADS TO SHOCK
- It is NOT SURPRISING that more than one mechanisms has evolved to control the excretion of Na
- When ECF volume is decreased, blood pressure falls:
  - **Glomerular capillary pressure declines and the GFR therefore falls, reducing the amount of Na filtered**
    - Tubular reabsorption of Na is increased, in part because the secretion of aldosterone is increased

DEFENSE OF SPECIFIC IONIC COMPOSITION:

- Special regulatory mechanisms maintain the levels of certain specific ions in the ECF as well as levels of glucose and other nonionised substances
- The feedback of Ca2+ on the parathyroids and the calcitonin-secreting cells to adjust their secretion maintains the ionised calcium level of the ECF
- The mechanisms controlling Na and K content are part of those determining the volume and tonicity of ECF and are discussed above
  - The levels of these ions are also dependent on the H+ concentration

DEFENSE OF H+ CONCENTRATION:

- The machinery of the cells is very sensitive to changes in H+ concentration

- Intracellular H+ concentration is different from extracellular pH and appears to be regulated by a variety of intracellular processes
- It is important to remember than the pH of blood is the pH of TRUE PLASMA – plasma that has been in equilibrium with red cells – because the red cells contain haemoglobin, which is quantitatively one of the most important blood buffers

H+ BALANCE:

- The pH of arterial plasma is 7.40 and that of venous plasma slightly lower
    - Technically ACIDOSIS is present whenever the arterial pH is below 7.40 and ALKALOSIS whenever it is above
        - Variations of up to 0.05 pH unit occur without untoward effects
        - Range that is compatible with life varies from 7.00- - 7.70
- Amino acids are utilised in the liver for gluconeogenesis, leaving as products NH_4^+ and HCO_3^- from their amino and carboxyl groups
    - The NH_4 is incorporated into urea and the protons that are formed are buffered intracellularly by HCO_3^-
    - HOWEVER, metabolism of sulphur containing amino acids produces H_2SO_4 and metabolism of phosphorylated amino acids produces H_3PO_4
        - These strong acids enter the circulation and present a major H+ load to the buffers in the ECF
- **Amino acid metabolism produces ammonia, bicarb, and acids**
- The CO_2 formed by metabolism in the tissues is in large part HYDRATED TO H_2CO_3
    - However, most of the CO_2 is excreted in the lungs and only small quantities of the H+ remain to be excreted by the kidneys
- COMMON SOURCES OF EXTRA ACID LOADS ARE:
    - Strenuous exercise (LACTIC ACID)
    - Diabetic ketosis (ACETOACETIC ACID AND BETA-HYDROXYBUTYRIC ACID)
    - Ingestion of acidifying salts
    - Failure of diseased kidneys to excrete normal amounts of acid is also a cause of acidosis
- A more common cause of alkalosis is LOSS OF ACID from the body as a result of VOMITING OF GASTRIC JUICE rich in HCl
    - This is the equivalent of adding alkali to the body

<u>BUFFERING:</u>

THE HENDERSON-HADDELBALCH EQUATION:

- The general equation for a buffer system is:
    - $HA \rightleftarrows H^+ + A^-$
        - A^- represents ANY ANION and HA the undissociated acid
        - If an acid stronger than HA is added to a solution containing this system, the equilibrium is shifted to the LEFT

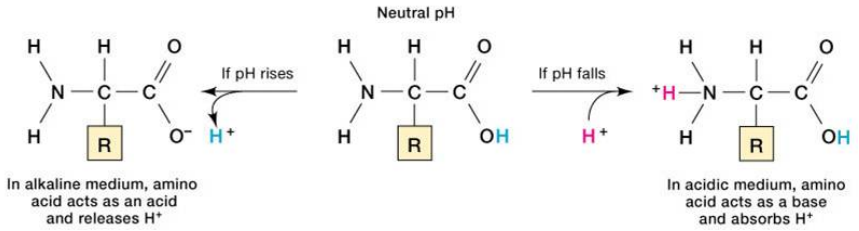
        - Hydrogen ions are thus TIED UP in the formation of MORE UNDISSOCIATED HA
    - If a base is added to the solution, H+ and OH- react to form H2O, but MORE HA DISSOCIATES
    - By the LAW OF MASS ACTION, the product of the concentrations of the products in a chemical reaction divided by the product of the concentration of the reactants at equilibrium is CONSTANT:
        - [H+][A-] / HA = K
        - If this equation is solved for H+ and put in pH notation, the RESULTING EQUATION IS THE **HENDERSON-HASSELBALCH EQUATION**
            - This describes the pH changes resulting from addition of H+ or OH- to any buffer system
            - **pH = pK +log [A-]/[HA]**
    - It is apparent from these equation that the **buffering capacity of a system is greatest when the amount of free anion is equal to the amount of undissociated acid**
        - **This is why the MOST EFFECTIVE BUFFERS IN THE BODY would be expected to be those with pK close to the pH in which they operate**

$$pH = pK_a + \log \frac{[A^-_{weak}]}{[HA_{weak}]}$$

BUFFERS IN BLOOD:

- **Blood buffering systems:**
    - **Plasma proteins (carboxyl & amino groups)**
    - **Haemoglobin (histidine residues)**
    - **Carbonic acid - bicarbonate**

- In the blood, proteins – especially the **PLASMA PROTEINS** – are effective buffers because both their **free carboxyl** and their **free amino** groups dissociate



- Another important buffer system is provided by the dissociation of the **IMIDAZOLE GROUPS OF THE HISTIDINE RESIDUES IN HAEMOGLOBIN**
    - The haemoglobin molecule contains 38 histidine residues
        - This plus the fact that haemoglobin is present in large amounts means that **haemoglobin in blood has SIX TIMES THE BUFFERING CAPACITY OF THE PLASMA PROTEINS**

- A third major buffer system in blood is the **CARBONIC ACID – BICARBONATE SYSTEM:**
    - $H_2CO_3 \rightleftarrows H^+ + HCO_3$
        - The pK for this system in an IDEAL SOLUTION is low (about 3)
            - However, in the body, H_2CO_3 is in equilibrium with CO_2 and the **pK for this reaction is 6.1**
        - The pK of this system is still low relative to the pH of the blood, but the system is one of the most effective buffer systems in the body because the amount of dissolved CO_2 is CONTROLLED BY RESPIRATION
        - In addition, the plasma concentration of HCO_3 is regulated by the kidneys
    - When H^+ is added to the blood, HCO_3 declines as more H_2CO_3 is formed
        - If the extra H_2CO_3 were not converted to CO_2 and H_2O and the CO_2 excreted in the lungs, the H_2CO_3 concentration WOULD RISE
        - An H^+ rise stimulates respiration and therefore produces a drop in PCO_2, so that some addition H_2CO_3 is removed
    - The reaction of $CO_2 + H_2O$ ->-< H_2CO_3 proceeds slowly in either direction unless the enzyme **CARBONIC ANHYDRASE** is present
        - There is abundant supply of this enzyme **in the red blood cells**

- The system $H_2PO_4^-$ ->-< $H^+ + HPO_4^{2-}$ has a pK of 6.80
    - In the plasma, the phosphate concentration is too low for this system to be a quantitatively important buffer
    - IT IS IMPORTANT INTRACELLULARLY
    - **Phosphate is an important intracellular buffer but plays little role extracellularly.**

SUMMARY:

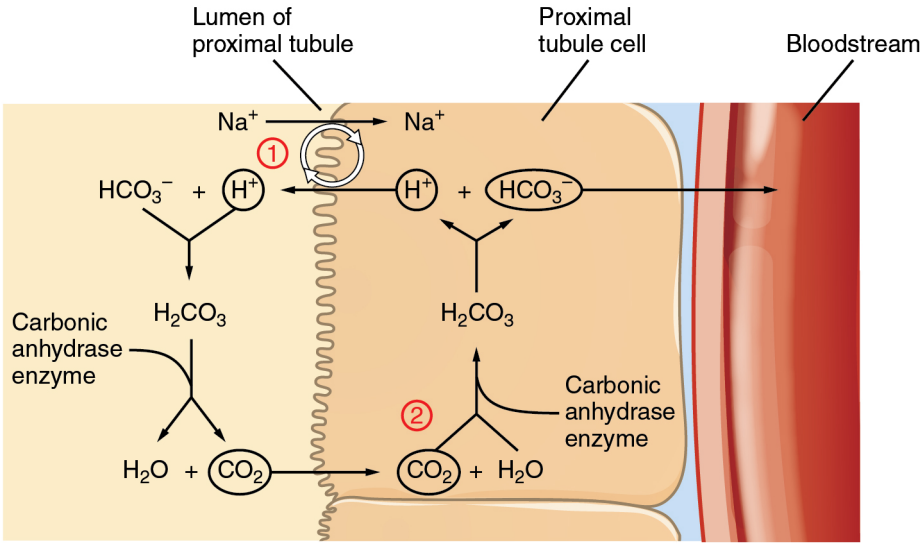
- When a strong acid is added to the blood, the major buffer reaction are driven to the left
    - The blood levels of the three "buffer anion" of haemoglobin, protein and HCO3 consequently drop
    - The anions are filtered into the renal tubules
        - They are accompanied by cations, particularly Na, because electrochemical neutrality is maintained
        - The tubules replace the Na with H+ and in so doing absorb equimolar amounts of Na and HCO3, thus conserving the cations and eliminating the acids

RESPIRATORY ACIDOSIS AND ALKALOSIS:

- A rise in arterial PCO2 due to decreased ventilation causes RESPIRATORY ACIDOSIS
    - The CO2 that is retained is in equilibrium with H2CO3, which in turn is in equilibrium with HCO3, so that the plasma HCO3 rises and a new equilibrium is reached at a lower pH
- A decline in PCO2 causes RESPIRATORY ALKALOSIS

RENAL COMPENSATION:

- HCO3 reabsorption in the renal tubules depends not only on the filtered load of HCO3, which is a PRODUCT OF THE GFR AND PLASMA HCO3, but also on the rate of H+ secretion by the renal tubular cells, since **HCO3 is reabsorbed in the kidney by exchange for H+**
- In respiratory acidosis, renal tubular H+ secretion is increased:
    - This is when PCO2 is high, the interior of most cells (including renal tubular cells) is more acidic
    - Also HCO3 reabsorption is increased
    - CL excretion is increased and plasma CL falls as plasma HCO3 is increased
- CONVERSELY:
    - In respiratory alkalosis, the low PCO2 hinders renal H+ secretion and HCO3 reabsorption is depressed and HCO3 is excreted, further reducing the already low plasma HCO3 and lowering the pH toward normal



METABOLIC ACIDOSIS:

- When acids stronger than HHb and the other buffer acids are added to blood, METABOLIC ACIDOSIS IS PRODUCED
- The H2CO3 formed is converted to H2O and CO2 and the CO2 is rapidly excreted via the lungs
- Also, the rise in H+ stimulates respiration, so that more CO2 is blown off
    - This RESPIRATORY COMPENSATION raises the pH even further

RENAL COMPENSATION:

- The anions that replace HCO3 in the plasma in metabolic acidosis are filtered, each with a cation (principally Na), thus MAINTAINING ELECTRICAL NEUTRALITY
- **Tubular cells secrete H+ into the tubular fluid in exchange for Na and for each H+ secreted, one Na and one HCO3 are added to the blood**
- The limiting urinary pH of 4.5 would be reached rapidly and the total amount of H+ secreted would be small if no buffers were present in the urine to "tie up" H+
- HOWEVER, secreted H+ reacts with
    - HCO3 to form CO2 and H2O (bicarbonate)
    - With HPO42- to form H2PO4- (phosphoric acid)
    - With NH3 to form NH4+ (ammonia)
- This allows large amounts of H+ can be secreted, permitting correspondingly large amounts of HCO2 to be returned to or added to the depleted body stores and large numbers of cations to be reabsorbed
- **When the acid load is very large, cations are lost with the anions, producing diuresis and depletion of body cation stores**
- **In chronic acidosis, glutamine synthesis is increased** and the glutamine provides the kidneys with an additional source of NH4

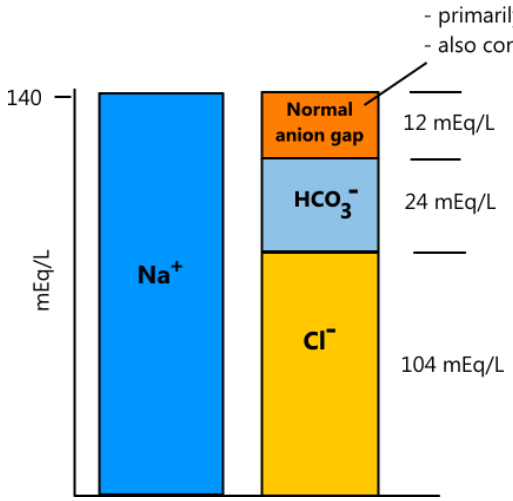
- Furthermore, the metabolism of glutamine in the kidneys produces alpha-ketoglutarate and this in turn is decarboxylated, producing HCO3, which enters the bloodstream and helps buffer the acid load

METABOLIC ALKALOSIS:

- The plasma HCO3 level and pH RISE
- The respiratory compensation is a DECREASE IN VENTILATION PRODUCED BY THE DECLINE IN H+ CONCENTRATION and this elevates the PCO2, bringing the pH back toward normal
  - The magnitude of this compensation is limited by the carotid and aortic chemoreceptor mechanisms
- More renal secretion of H+ is expended in reabsorbing the increased filtered load of HCO3

CLINICAL EVALUATION OF ACID-BASE STATUS:

- The PCO2 is 7-8mmHG higher and the pH 0.03-0.04 unit lower in VENOUS than ARTERIAL BLOOD because venous blood contains the CO2 being carried from the tissues to the lungs
- A measurement that is of some value in the differential diagnosis of metabolic acidosis is the **ANION GAP:**
  - **Refers to the difference between the concentration of CATIONS other than Na and the concentration of ANIONS other than Cl- and HCO3-**
    - It consists for the most part of:
      - **Proteins** in the anionic form
      - **Phosphate**
      - **Sulphate**
    - **NORMAL VALUE IS 12meq/L**
  - It is increased when the plasma concentration of K, Ca or Mg is decreased, when the concentration of or the charge on plasma proteins is increased or when organic anions such as lactate or foreign anions accumulate in blood
- The anion gap is INCREASED in metabolic acidosis due to:
  - Ketoacidosis
  - Lactic acidosis
  - Other forms of acidosis in which organic anions are increased



Anion gap = Na^+ - (Cl^- + HCO_3^-)

Corrected anion gap for hypoalbuminemia =
(4 - serum albumin concentration) X 2.5 + calculated anion gap

Reference [1,2,5]