Acid Base Regulation

pH

- Definition of pH
    - Negative logarithm of H expressed in mol/L
        - pH = -loh H+ so that H = 10 $^{-pH}$
- pH values in the body
    - ECF = 7.4
    - Cell = 7.2
    - Blood
        - Arterial = 7.4
        - Venous = 7.36
            - Lower because of CO2
    - Balance
        - Normal 7.35-7.45
        - Acidotic <7.35
            - <6.8 is fatal
        - Alkalosis >7.45
            - >8.0 is fatal
- Biological importance
    - Enzymes function maximally at 7.2
    - High or low pH denatures proteins
    - H+ competes with Ca for binding
        - Important for regulating membrane potential

Uncontrolled input and outputs of acid and base

- Net acid input
    - Complete
        - Most from Carbon dioxide
            - Produced by all cells that use aerobic metabolism to produce ATP
            - 12-15 Mol/day
            - Via metabolism of all food groups
        - Sulphuric acid
            - From metabolism of sulphur containing amino acids
        - Urea
            - From amino acids with cationic side groups
        - Phosphoric acid
            - From phospholipids and phosphorylated proteins
    - Incomplete
        - Lactate
            - Carbohydrates in anaerobic exercise
        - Ketoacids
            - Fats from high fat diets - in diabetics
- Net base input
    - Complete
        - Bicarbonate
            - Amino acids with anionic side groups
            - Organic anions - citrate and ascorbate
- Diet
    - Protein rich
        - Acid excess
    - Vegetable diet
        - Base excress
- Illness
    - Vomiting
        - Causes loss of HCl

        - More basic
    - Diarrhoea
        - Loss of bicarbonate
        - Increase in pH

Homeostasis of pH
- Short term
    - Seconds
        - Immediate neutralisation by buffers
    - Minutes
        - Continuous removal of $CO2$ by the lungs
    - Hours - days
        - Maintenance of bicarbonate by the kidneys
- Long term
    - Input of excess acid/base = output of acid/base

Acids
- Acids are H+ donors, bases are H+ acceptors
    - Acid -> Base + H+
- Strong acids
    - Dissociates completely in water
        - Eg HCl is added to water to give a 1 mM concentration
            - H+ + Cl^- so H=1mM = 10^{-3} M and pH = 3
- Weak Acids
    - Only partially dissociate to give varying concentrations of the conjugate acid/base pair
    - Equilibrium constant for each conjugate acid/base pair
        - K_a = [base] x [H+]/ [acid]
            - K_a - acid dissociation constant
    - Henderson Hasselbalch equation
        - pH = pK_a + log [base]/[acid]
        - Eg phosphate buffers
            - H_2PO_4 -> HPO_4^2 + H+
            - pH = 6.8 + log [HPO_4^{2-}]/[$H_2PO_4^-$]
        - If the number mM of both acid and base are the same
            - pH will be the same as pKa
            - pH = 6.8 + log 5/5 = 6.8

Buffers
- Add 1 mM NCl to the phosphate buffer - started off with 5 mM of both base and acid
    - H_2PO_4 -> HPO_4^2 + H+
    - pH = 6.8 + log 5-1/5+1 = 6.62
- Adding 1mM of HCl
    - Changes water from 7 to 3 = 4 pH units
    - Changes phosphate buffer from 6.8 to 6.62
        - 0.18 pH units
- Determinants of buffering capacity
    - Change in pH when add 1mM HCl to 10 mM of phosphate buffer
    - When initial pH = pKa
        - Change from 6.8 to 6.62
            - 0.18 pH units
    - When initial pH = pKa + 2
        - Change from 8.8 to 7.71
            - 1.1 pH units

    - Buffering capacity is high when
        - Buffer concentration is high
        - Starting pH = pKa
- ECF buffers
    - Bicarbonate system
        - Bicarbonate / CO_2 pair
        - Proteins - haemoglobin and albumin
        - CO_2 + H_2O <-Carbonic Anhydrase-> H+ HCO_3
        - OHb + H <-> HHb + O_2

- HH equation
  - pH = pKa + log[HCO3] / S x pCO2
    - HCO3 = 24mM
    - pCO2 = 40 mmHg
    - pKa = 6.1
    - S = 0.03mmol
  - pH = 6.1+log 24/0.03x40=6.1+log 24/1.2 = 7.4
- Buffers all body acids except CO2
- Highly effective because
  - Plasma carbonate is high
  - Operates in conjunction with haemoglobic
  - Regulated open system
    - No conservation of mass
    - Much more effective than closed
      - 25.2 mM total carbonate for closed - also you die
      - 13.2mM for open
        - Breathe off CO2 excess
        - Kidney's regulate bicarb

pH stabilisation by the kidney

- HCO3 is consumed as it buffers the non carbonic acids
- $H_2O + CO_2 + HPO_4^{2-} \leftrightarrow HCO_3^- + H_2PO_4^-$
- Role of the kidney is to ensure that
  - Filtered HCO3 is reabsorbed
  - Additional molecules are produced
- Excess HCO3 is removed by reducing reabsorption
- Renal mechanisms
  - Reabsorption of filtered HCO3
    - In proximal tubule
      - Bicarb enters tubular
        - As sodium bicarbonate
          - Sodium moves down concentration gradient into the cell
          - The energy moves H+ into fluid from cell
            - Secondary active transport - antiport
            - H+ binds with HCO3
              - = H2O + CO2
              - Both move into cell - combines
                - Produces H+
                  - Goes into fluid
                - And HCO3
                  - Moves into peritubular capillaries
                    - With sodium
                    - Secondary active transport - symport
    - In collecting duct
      - Mostly the same
      - Uses pump as H+ concentration gradient is high
        - Needs ATP
      - Exchange of Cl and HCO3 into blood
  - HCO3 regeneration with excretion of titratable acids
    - Proximal tubule
      - 2Na + HPO4
        - Sodium moves into cell
        - H+ moves out

- H+ is buffered by base HPO_4
  - Acid H_2PO_4 is excreted
- H+ is produced from H_2O and CO_2
  - Also HCO_3
    - Moves into blood with sodium symport

- HCO3 regeneration with NH4 excretion
    - In proximal tubule
        - Glutamine is metabolised
            - Makes 2NH4
                - Antiport with Na
                - Excrete NH4
            - Converts to ketogluterate
            - Then converted to glucose
                - Via gluconeogeneris
                - By consuming 2 H+
                    - Produced from 2x H2O + CO2
                        - Also produces 2HCO3
                            - Moves into blood with Na symport
    - Long term method
- Control
    - Decreased body pH increases H+ secretion
        - Needed to reabsorb HCO3
    - Decreased body pH increases glutamine uptake
        - For producing new bicarb

Disturbances of Acid Base Balance

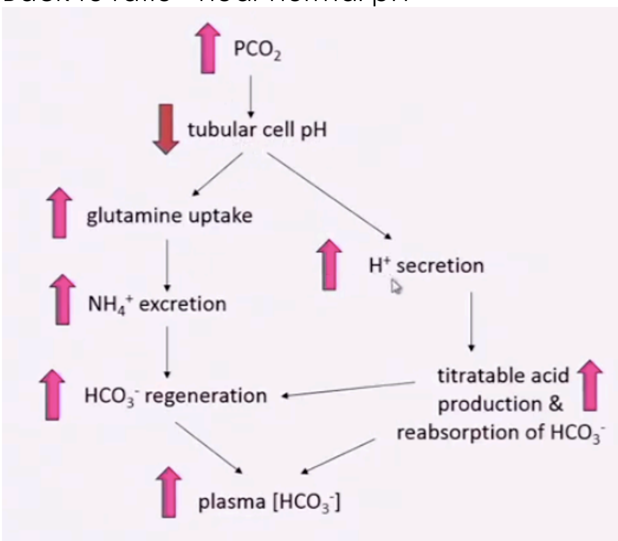
Balance

- Arterial blood pH
    - Between 7.35-7.45
- Arterial plasma HCO3
    - 22-26mM
- Arterial pCO2
    - 35-45mmHg
- To be in balance all three must be in normal range

Disturbances

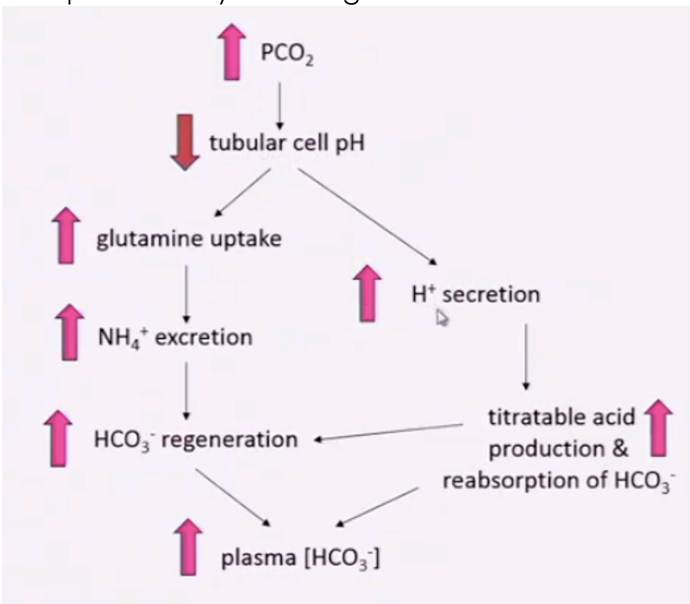
- pH = pKa + log HCO3/S x CO2
- Fixed via
    - Buffering
        - By haemoglobin, plasma proteins, phosphates
        - Can't be buffered by carbonate
            - Can't buffer itself
    - Compensatory changes
        - Shift HCO3/CO2 ratio (so pH) back towards normal
            - Even though cause has not been fixed
    - Correction
        - Need to correct problem to return to balance
- Respiratory
    - Acidosis
        - Increase in pCO2
        - From hypoventilation - shallowing breathing
            - Lung diseases
                - Emphysema
                - Airway obstruction or chest injury
                - Inhibited respiratory drive
                    - In brainstem - respiratory centres
                    - Brain injury
                    - Drugs
                        - Morphine, heroin, anaesthetics
        - Effect on pH

- Law of mass action
    - Carbonate buffering equation is shifted to the right
        - H+ increases, pH decreased

      - Increase in CO_2
        - Decreases HCO_3/CO_2 ratio
          - = decrease in pH
          - = acidosis
    - If CO_2 increases, shouldn't HCO_3 increase
      - At pH 7.4
        - HCO_3 - 24mM
        - H+ $10^{-7.4}$ = 40nM
      - If CO_2 doubles
        - Ka = $2(HCO_3 \times H+)/2(CO_2)$
        - Reaction continues until 40nM of CO_2 and H_2O combines
          - Giving an 40nM of both HCO_3 and H+
          - H+ is doubled - new steady state is reached
          - HCO_3 is unchanged
        - Though not necessarily true in the body
          - Bc buffers
    - Compensation
      - Kidney increases plasma HCO_3
        - Back to ratio - near normal pH
        - 

        - Can take hours to days
      - But balance not restored until hypoventilation is corrected
  - Alkalosis
    - Decreased CO_2
    - From hyperventilation
      - High altitudes
      - Sepsis, fever, brain damage, hysteria
      - Pregnancy
    - pH increased by reduced CO_2
      - Increased ratio
    - Kidney compensates by reducing HCO_3
      - Decrease reabsorption
      - Increase pH inhibits H+ secretion from tubular cells
        - Less of filtered HCO_3 is reabsorbed
        - Plasma HCO_3 falls
    - But HCO_3 and CO_2 is low so not in balance
- Metabolic
  - Acidosis
    - Decrease in HCO_3

- From
  - Diarrhoea
  - Strenuous anaerobic exercise
  - Ketoacidosis
  - Renal failure

- pH decreased by reduced HCO_3
  - Decreased ratio
- Lung compensates by reducing CO_2
  - 

- Alkalosis
  - Increase in HCO_3
  - Due to vomiting
    - Losing acid from stomach
      - So replace acid from lining in the stomach
        - Create H+ but also HCO_3
          - Pump the H+ into stomach
          - HCO_3 goes into blood
  - pH increased by increased HCO_3
    - Increased ratio
  - Lungs compensate by increasing CO_2
  - But if we can just decrease HCO_3 by not reabsorbing why does this occur
    - Bc when vomiting -
      - Causes dehydration
      - Expel Na and K
        - HCO_3 can only be excreted with Na - its counter ion
        - Na decrease - RAAS system activated - Na reabsorption increased
          - HCO_3 excretion stopped - and starts reabsorbing
      - Cannot be corrected until body Na is restored

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	pH	Primary Change	Compensatory change
Resp Acid	Low	CO2 high	HCO3 high
Resp Alk	High	CO2 low	HCO3 low
Met Acid	Low	HCO3 low	CO2 low
Met Alk	High	HCO3 high	CO2 high