Acid – base balance

Acids vs. Bases

- Normal A:B ratio ~ 1:20
- Acid: a substance that may donate protons (hydrogen ions)
- Base: a substance that may receive protons
- strength is defined in terms of the tendency to donate (or accept) the hydrogen ion to (from) the solvent (i.e. water in biological systems)

pH

- pH is an indirect measure of $[H^+]$

$$pH = -\log [H^+]$$

Hydrogen ions (i.e. protons) do not exist free in solution but are linked to adjacent water molecules by hydrogen bonds (H_3O^+)

  - $[H^+]$ by a factor of 2 causes a ↓ pH of 0.3

- Neutral vs. normal plasma pH
  - pH 7.4 (7.36-7.44) → normal
  - pH 7.0 → neutral but fatal!!!

pH 7.40 ~ 40 nM
pH 7.00 ~ 100 nM
pH 7.36 ~ 44 nM
pH 7.44 ~ 36 nM

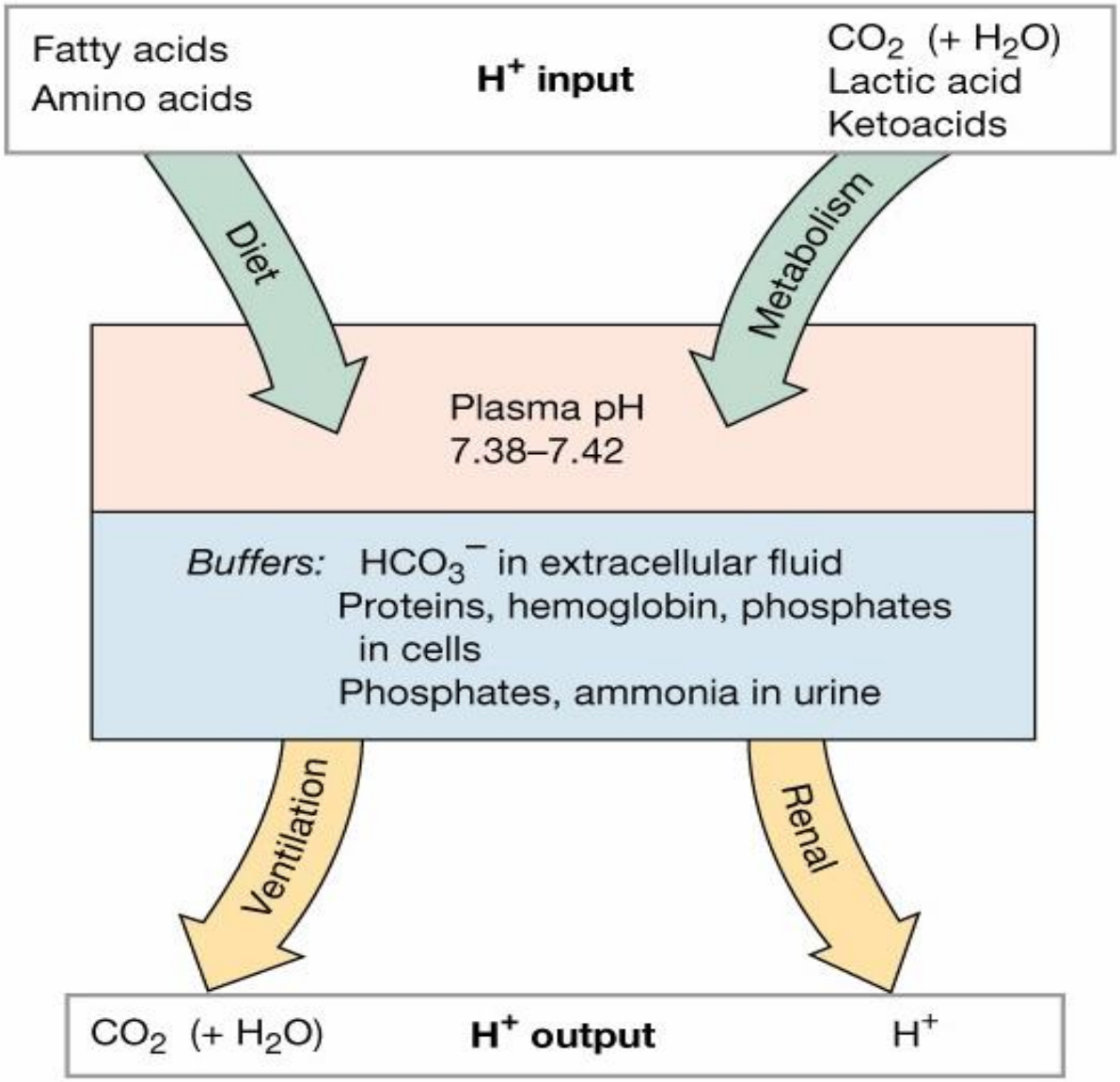
Buffers

- Extracellular
  - carbonic acid / bicarbonate (H_2CO_3 / HCO_3^-)

Henderson-Hasselbalch equation:
$pH = 6.1 + \log([HCO_3^-] / 0.03\ pCO_2)$
MODIFIED HENDERSON: $[H^+] = 24 * PCO_2/[HCO_3^-]$

- Haemoglobin

- Intracellular
  - proteins
  - phosphoric acid / hydrogen phosphate (H_3PO_4 / $H_2PO_4^-$ + HPO_4^{2-})


Fatty acids
Amino acids
H+ input
CO2 (+ H2O)
Lactic acid
Ketoacids
Diet
Metabolism
Plasma pH
7.38–7.42
Buffers: HCO3− in extracellular fluid
Proteins, hemoglobin, phosphates in cells
Phosphates, ammonia in urine
Ventilation
Renal
CO2 (+ H2O)
H+ output
H+

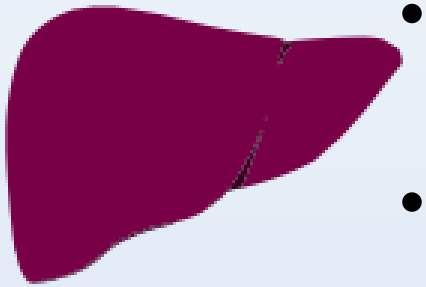
Organs involved in the regulation of A-B-balance

- Equilibrium with plasma
- High buffer capacity
  - Haemoglobin – main buffer for CO_2

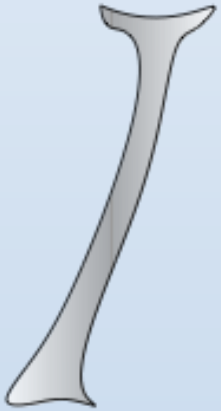
- Excretion of CO_2 by alveolar ventilation: minimally 12,000 mmol/day

- Reabsorption of filtered bicarbonate: 4,000 to 5,000 mmol/day
- Excretion of the fixed acids (acid anion and associated H^+): about 100 mmol/day

Organs involved in the regulation of A-B-balance

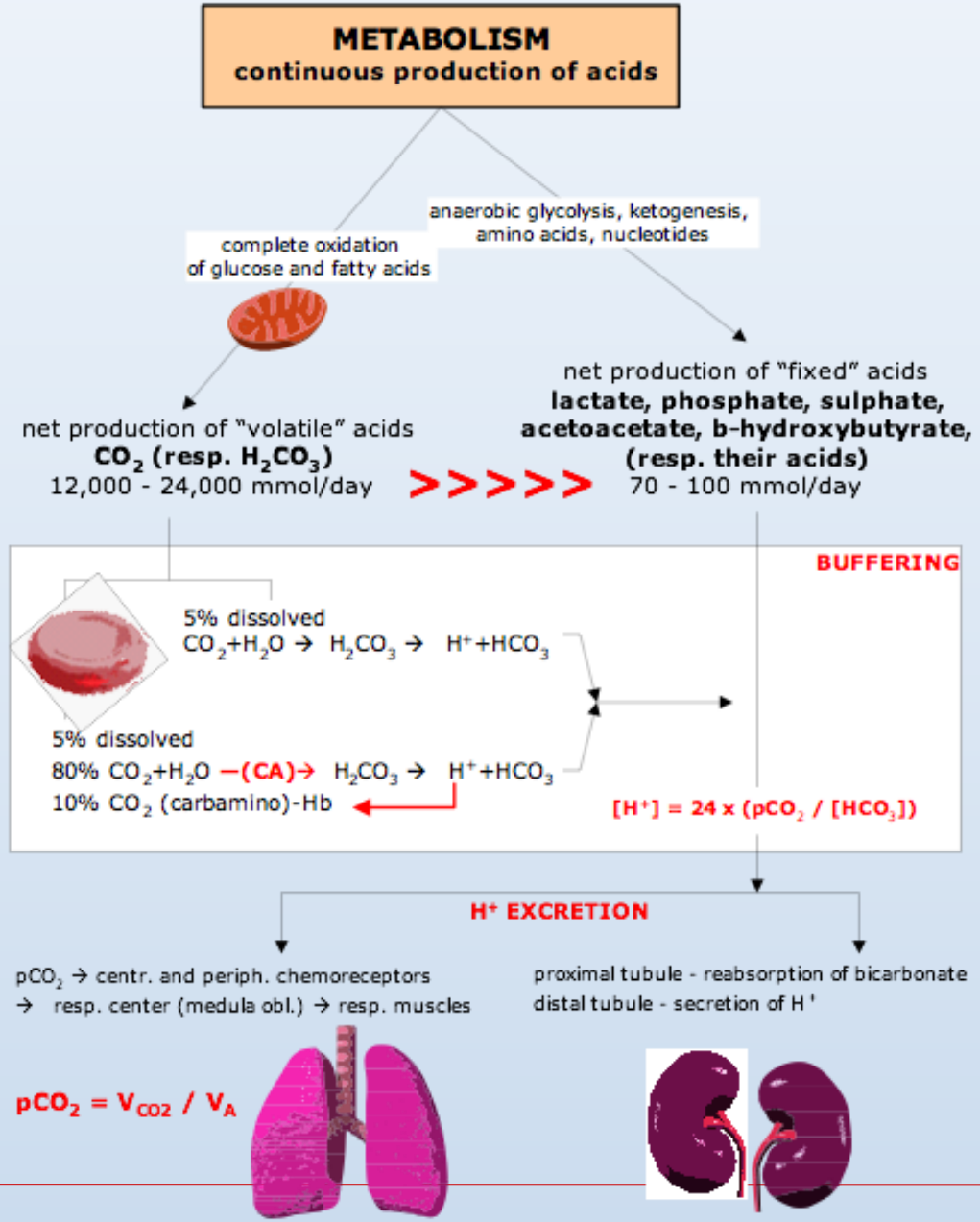


- CO_2 production from complete oxidation of substrates
  - 20% of the body's daily production
- metabolism of organic acid anions
  - such as lactate, ketones and amino acids
- metabolism of ammonium
  - conversion of NH_4^+ to urea in the liver results in an equivalent production of H^+
- Production of plasma proteins
  - esp. albumin contributing to the anion gap



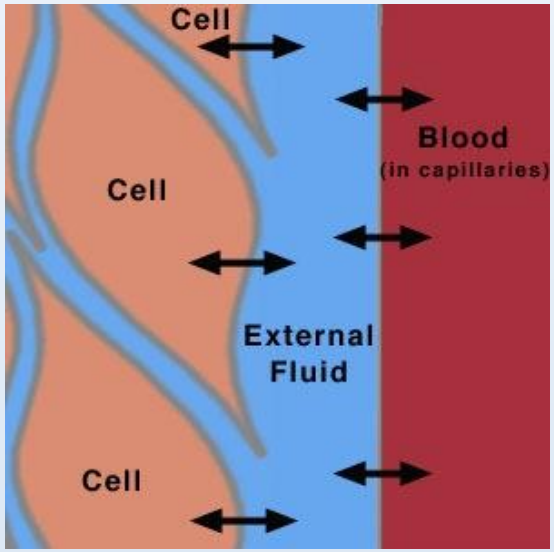
- Bone inorganic matrix consists of hydroxyapatite crystals ($Ca_{10}(PO_4)_6(OH)_2$]
  - bone can take up H^+ in exchange for Ca^{2+}, Na^+ and K^+ (ionic exchange) or release of HCO_3^-, CO_3^- or HPO_4^{2-}

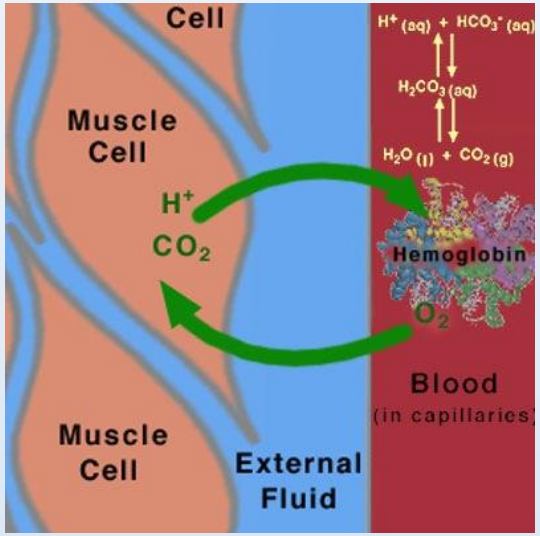
Metabolism affects PH continuously



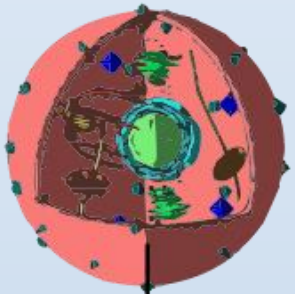
Total CO_2:
= $[HCO_3]$ + $[H_2CO_3]$
+ [carbamino CO_2]
+ [dissolved CO_2]

The most important pH for the body is the intracellular pH





In assessment of acid-base disorders, the clinician is always looking from the outside ir



we use the extracellular results to make inferences about the intracellular conditions

The most important pH for the body is the intracellular pH

- Intracellular pH is maintained at about the pH of neutrality (~6.8 at 37°C) because this is the pH at which metabolite intermediates are all charged and trapped inside the cell

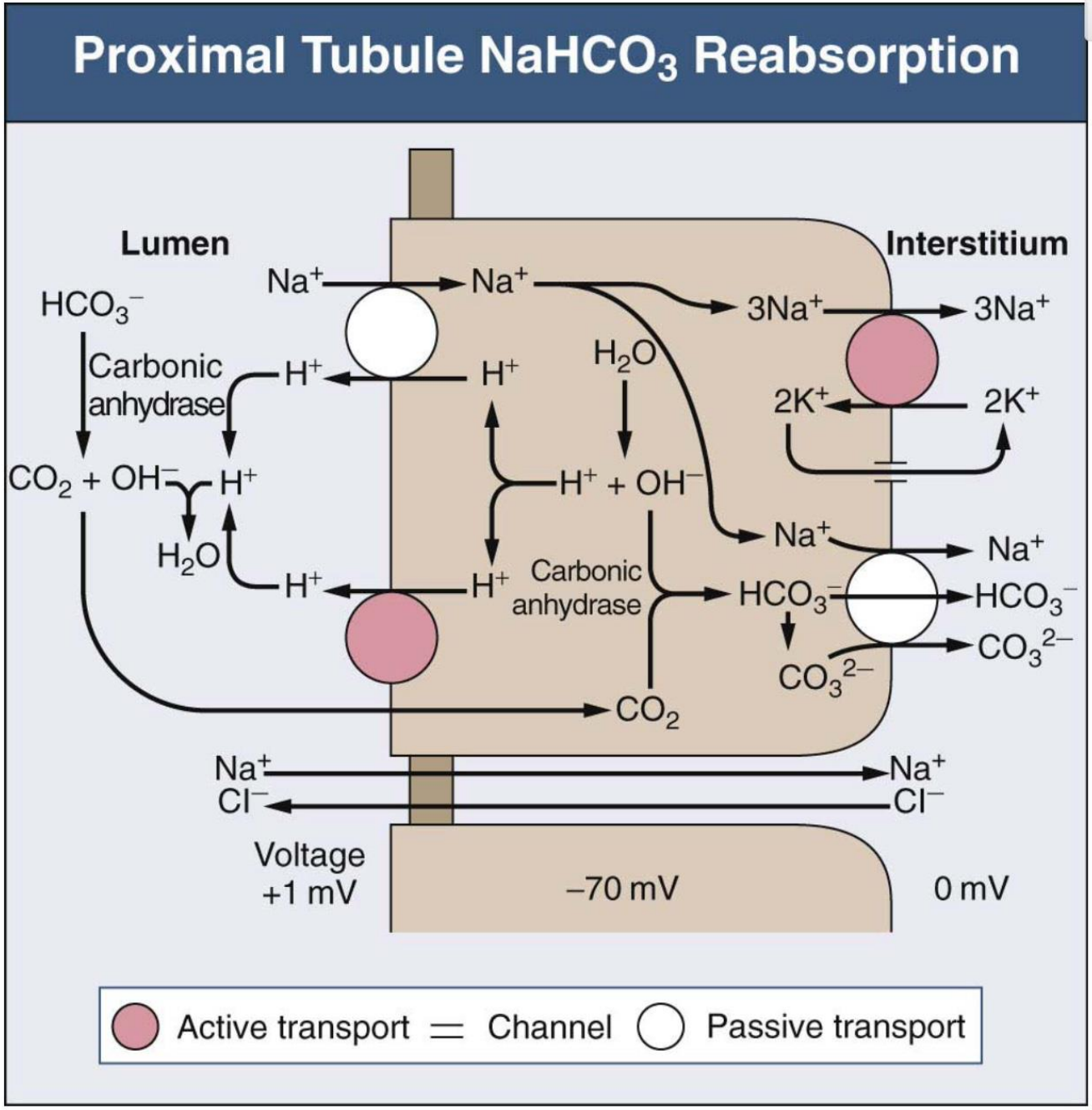
- Extracellular pH is higher by 0.5 to 0.6 pH units and this represents about a Fourfold gradient favouring the exit of hydrogen ion from the cell
  - To maintain it at a stable value because of the powerful effects of intracellular [H+] on metabolism
  - maintaining a stable intracellular pH by:
    - 'Intracellular buffering' (chemical, metabolic, organelles)
    - Adjustment of arterial pCO_2
    - Loss of fixed acids from the cell into the extracellular fluid

Respiratory system - CO_2

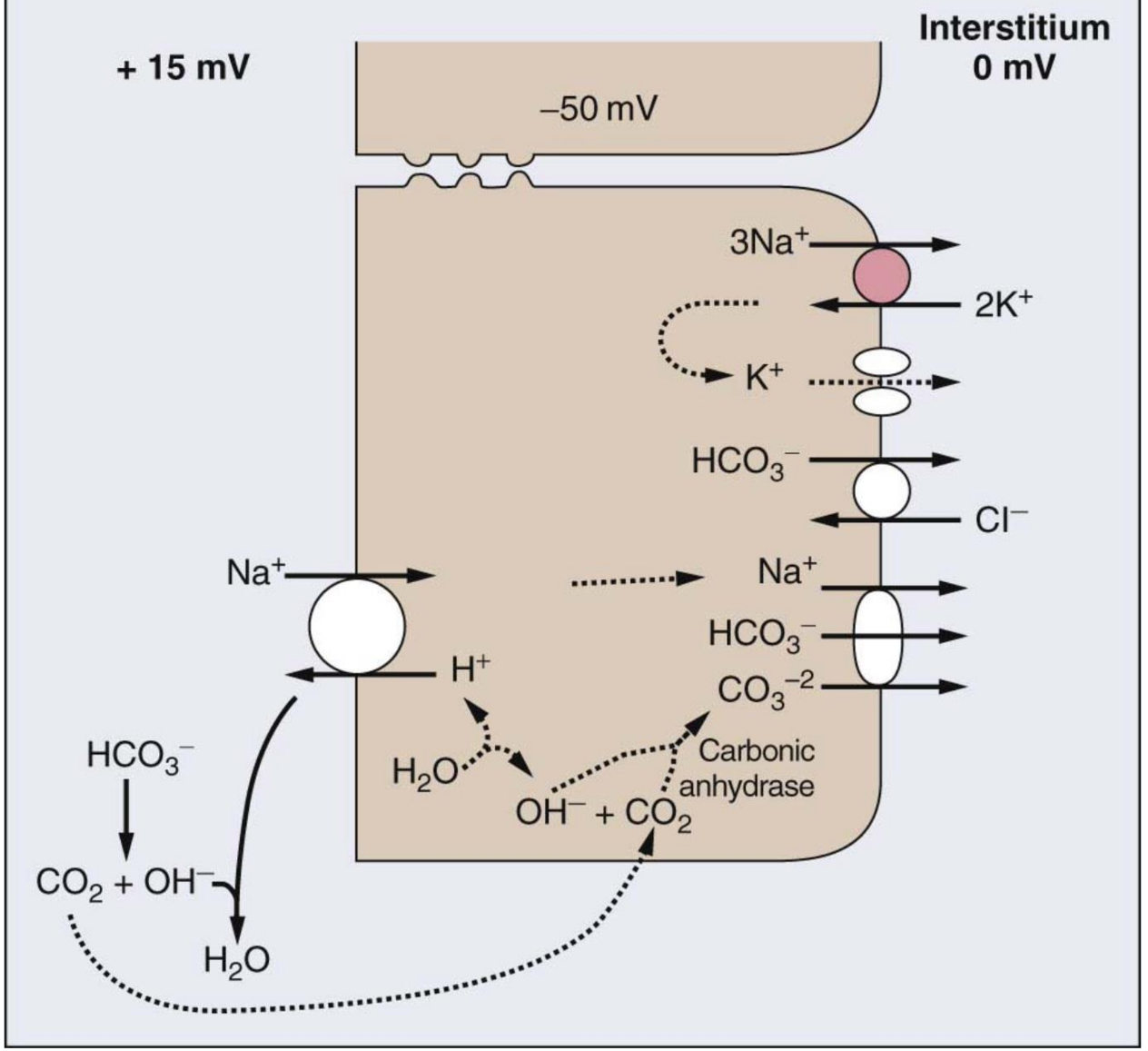
- Differences in the stimulation of respiration by pCO_2, H^+ and pO_2
- Alveolar ventilation
- Disturbances
  - acidemia
    - → respiratory center of the brain
    - → alveolar ventilation
    - → ↓CO_2
  - alkalemia
    - → respiratory center of the brain
    - → ↓ alveolar ventilation
    - → CO_2

Renal system – fixed H^+ & HCO_3^-

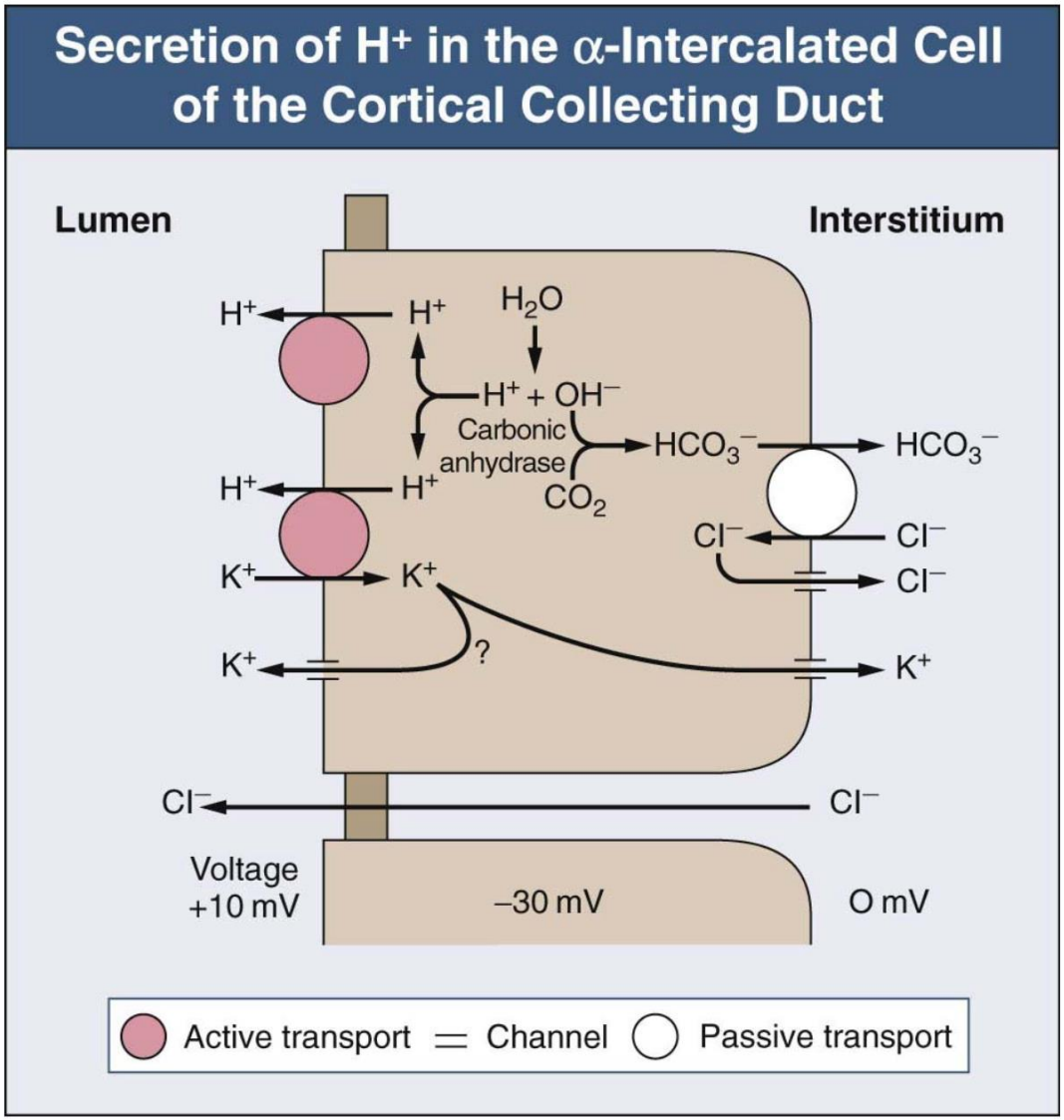
- Proximal tubular mechanisms:
  - Reabsorption of HCO_3^- filtered at the glomerulus
  - Production of NH_4^+
- Distal tubular mechanisms:
  - net excretion of H^+
    - normally 70mmol/day
    - max. 700mmol/day together with proximal tubule excretion of H^+ could increase up to 1000x!!! (↓pH of urine 4.5)
  - Formation of titratable acidity (TA)
  - Addition of NH_4^+ to luminal fluid
  - Reabsorption of remaining HCO_3^-

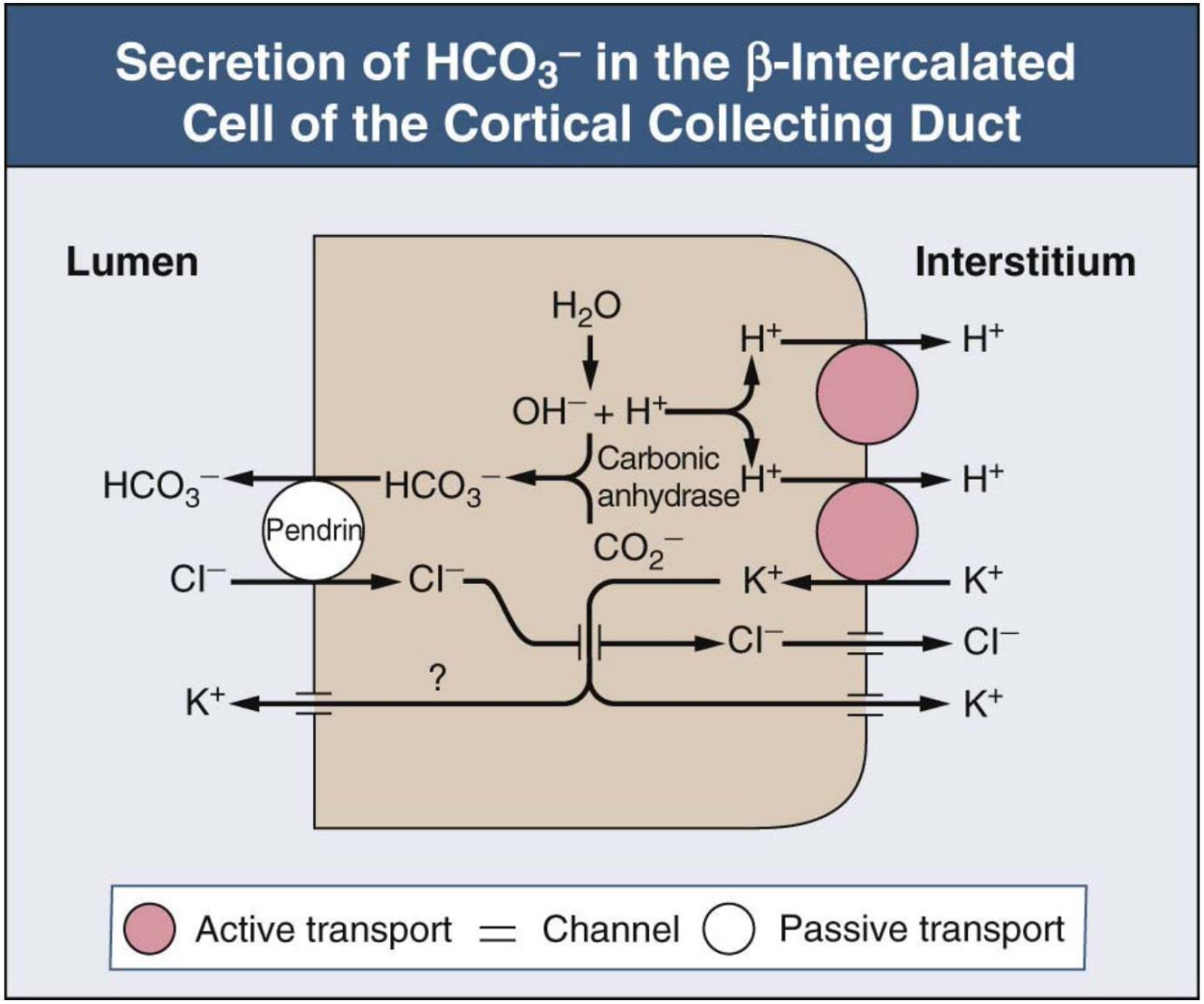

Proximal Tubule NaHCO3 Reabsorption
Lumen
Interstitium
HCO3−
Carbonic anhydrase
CO2 + OH−
H+
H2O
Na+
Na+
H+
H+
H2O
H+ + OH−
H+
H+
Carbonic anhydrase
CO2
3Na+
3Na+
2K+
2K+
Na+
Na+
HCO3−
HCO3−
CO3 2−
CO3 2−
Na+
Cl−
Na+
Cl−
Voltage
+1 mV
−70 mV
0 mV
Active transport
Channel
Passive transport

Thick Ascending Limb

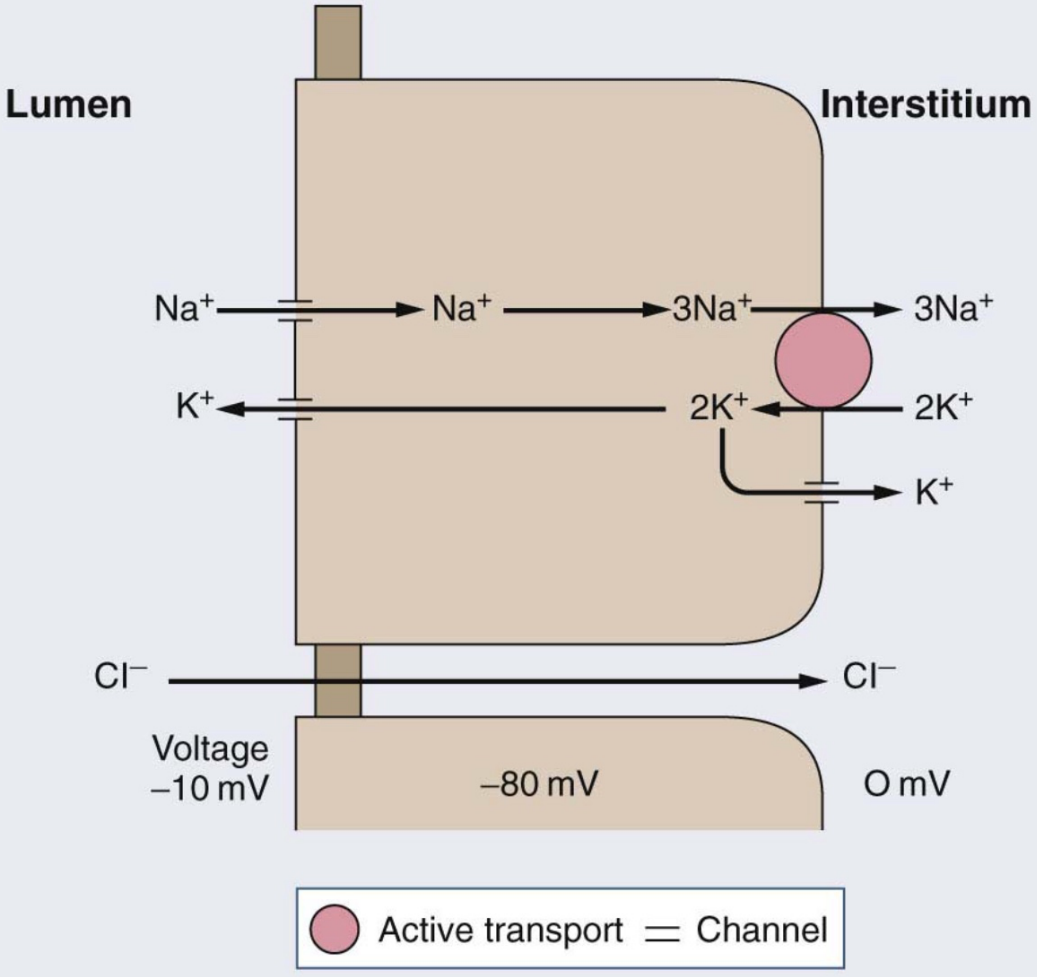


Secretion of H^+ in the α-Intercalated Cell of the Cortical Collecting Duct




Secretion of HCO_3^- in the β-Intercalated Cell of the Cortical Collecting Duct
Lumen
Interstitium
H_2O
$OH^- + H^+$
Carbonic anhydrase
H^+
H^+
H^+
H^+
HCO_3^-
HCO_3^-
Pendrin
CO_2^-
Cl^-
Cl^-
K^+
K^+
Cl^-
Cl^-
?
K^+
K^+
Active transport
Channel
Passive transport

Transport of Na^+ in the Principal Cell of the Cortical Collecting Duct



Overall, the kidneys must excrete H^+ and prevent the loss of HCO_3-.

Filtered HCO_3^- must react with secreted H^+ in order to be reabsorbed as H_2CO_3

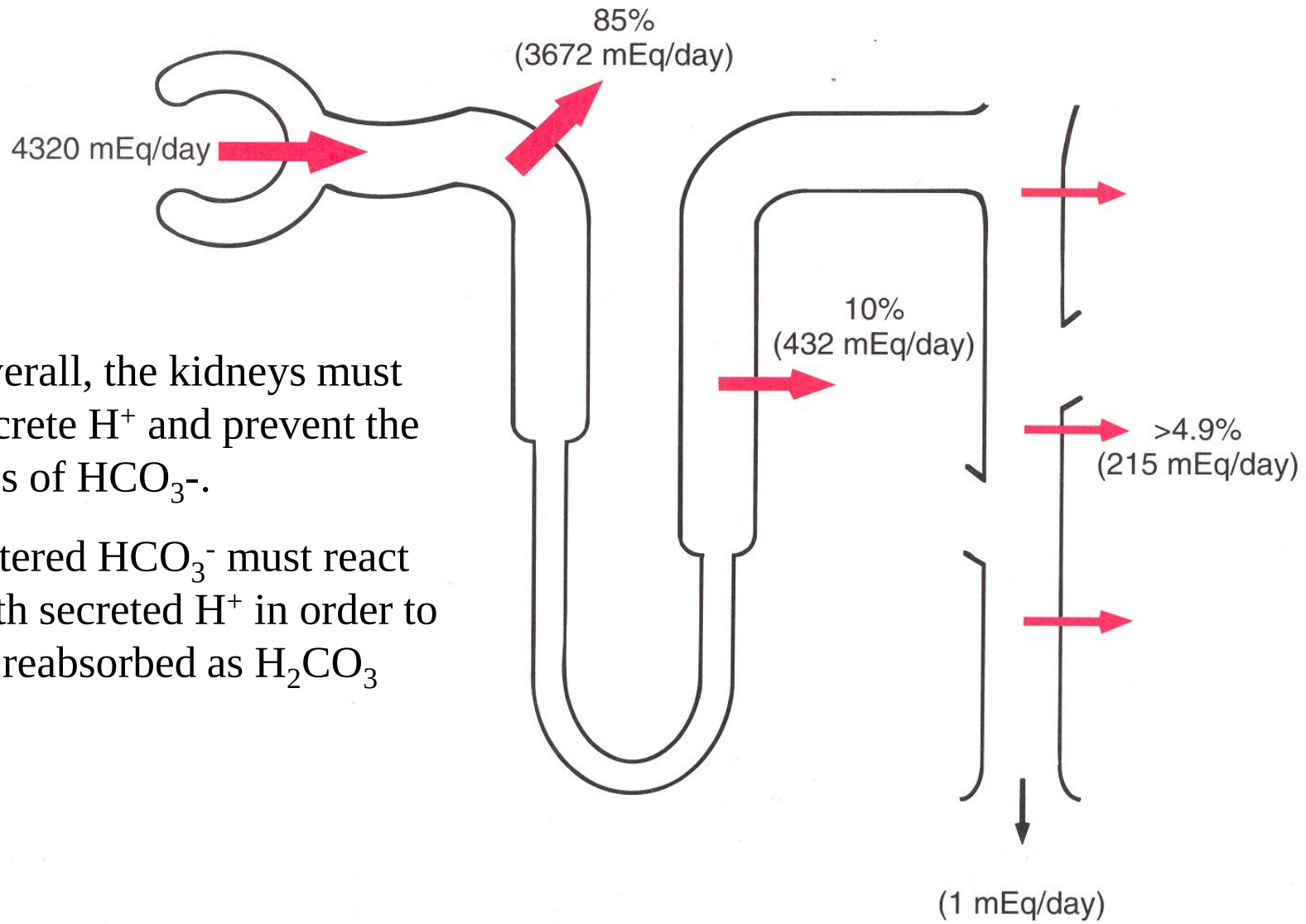


Figure 30–4. Reabsorption of bicarbonate in different segments of the renal tubule. The percentages of the filtered load of bicarbonate absorbed by the various tubular segments are shown as well as the number of milliequivalents reabsorbed per day under normal conditions.

PROXIMAL H+

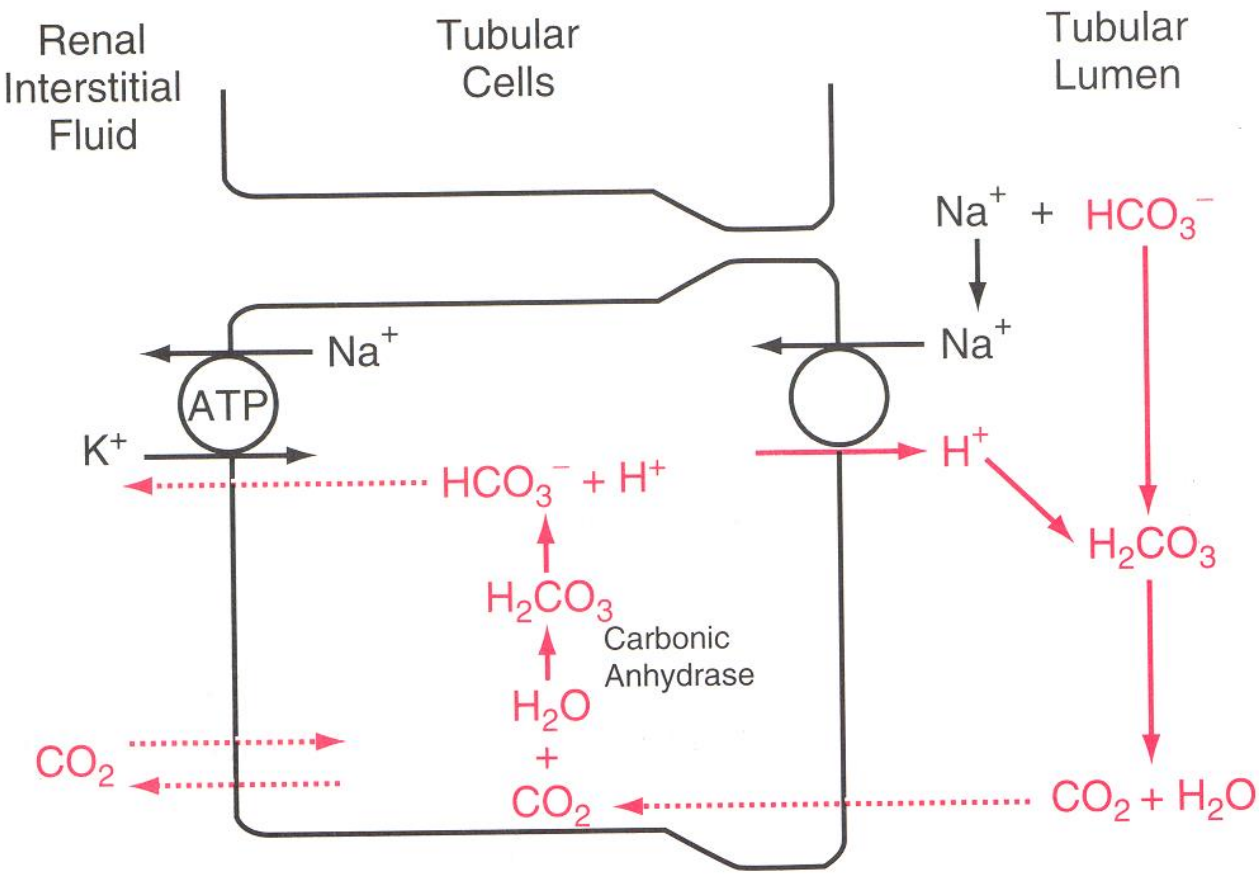


Figure 30–5. Cellular mechanisms for (1) active secretion of hydrogen ions into the renal tubule; (2) tubular reabsorption of bicarbonate by combination with hydrogen ions to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange for the hydrogen ions secreted. This pattern of hydrogen ion secretion occurs in the proximal tubule.

H+ is secreted via a Na-H counter-transport process, coupled to the active movement of Na into the cell *via* the basalateral Na-K ATPase.

HCO_3^- reabsorption is facilitated by the enhanced conversion of CO_2 to H_2CO_3 (normally slow) *via* the enzyme carbonic anhydrase

DISTAL H+

In the intercallated cells of the distal tubule, a H/Cl co-transport is involved with H+ secretion.

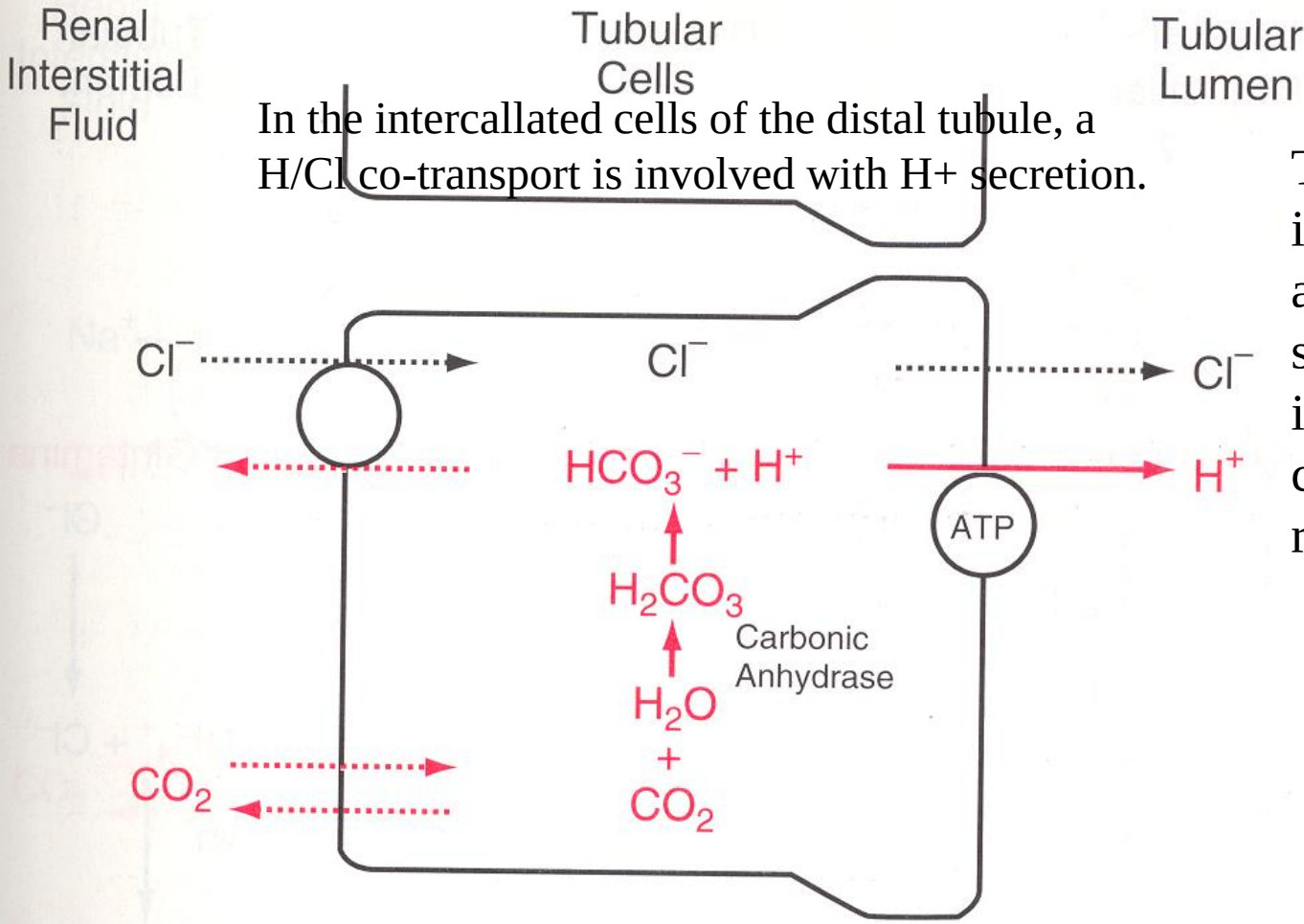
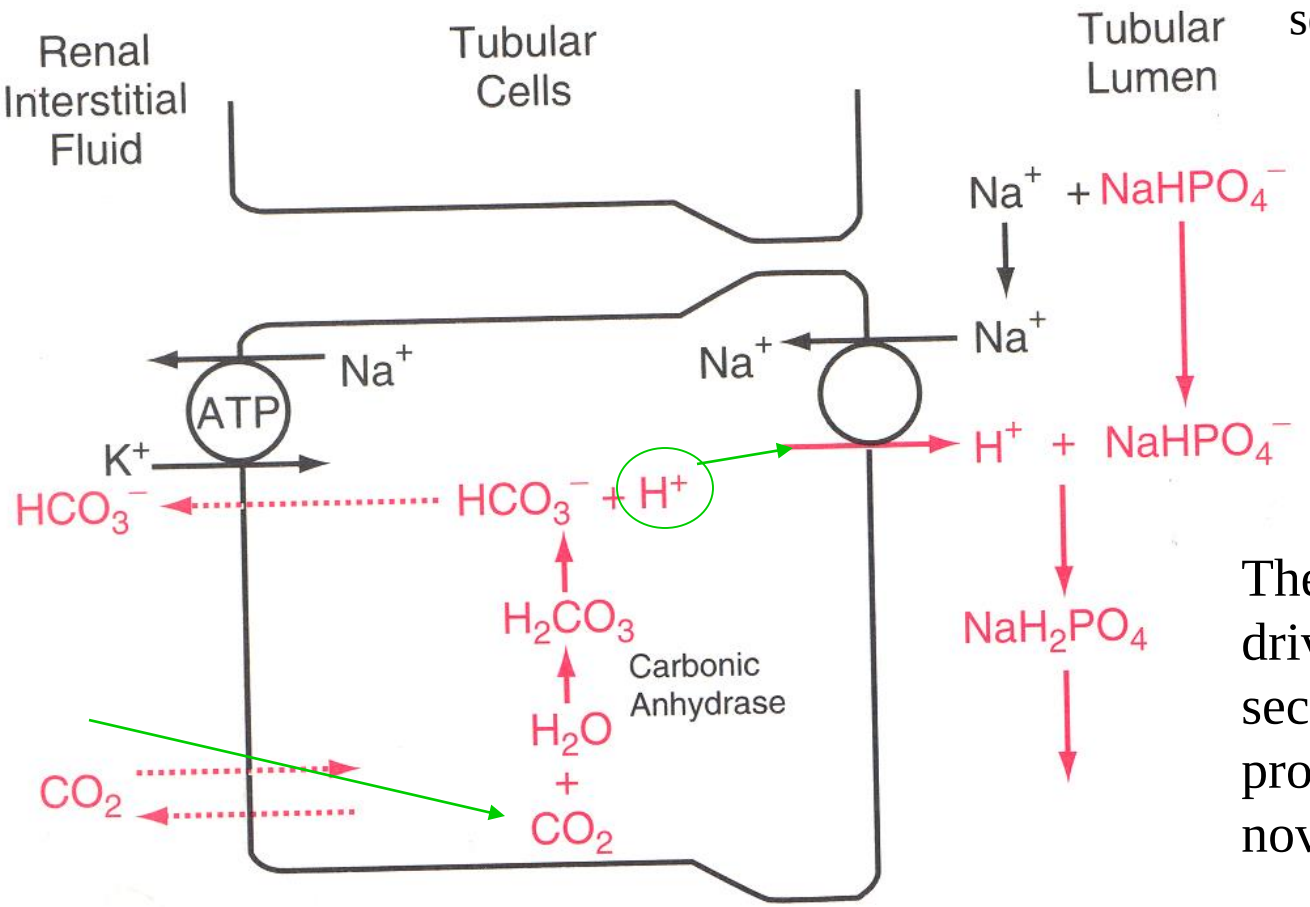


Figure 30–6. Primary active secretion of hydrogen ions through the luminal membrane of the epithelial cells of the distal and collecting tubules. Note that one bicarbonate is absorbed for each hydrogen ion secreted and a chloride ion is passively secreted along with the hydrogen ion. This pattern of hydrogen ion secretion occurs in the intercalated cells of the late distal tubules and collecting tubules.

The formation of H^+ inside the cell provides a gradient for the secretion of more H+ into the lumen to complex with and reabsorb more HCO_3^-

This distal pathway accounts for only 5% of secreted H+ but the H+ gradient it can form is 900X so it is a major site for creating an acidic urine pH 4.5

Phosphate buffering and secretion of H+



The process of driving CO2 to secrete a H+ produces HCO_3 de-novo

Figure 30–7. Buffering of secreted hydrogen ions by filtered phosphate ($NaHPO_4^-$). Note that a new bicarbonate is returned to the blood for each $NaHPO_4^-$ that reacts with a secreted hydrogen ion.

AMMONIUM GENERATES HCO_3^-

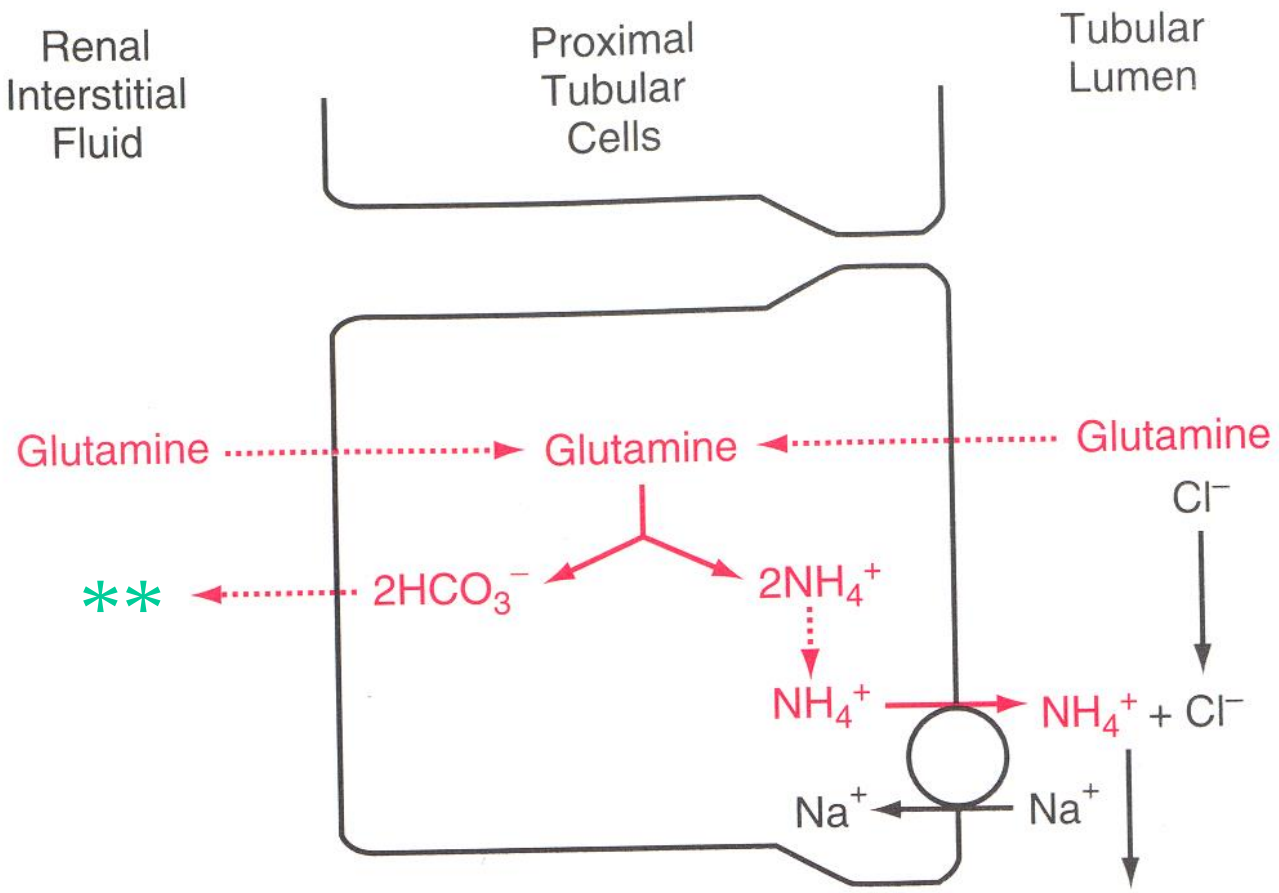


Figure 30–8. Production and secretion of ammonium (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and bicarbonate. The ammonium ion (NH_4^+) is actively secreted into the lumen by means of a sodium-NH_4^+ pump. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted and two HCO_3^- are returned to the blood.

Ammonium (NH_4^+) is produced from the cellular metabolism of glutamine in all nephron segments. Ammonium is secreted into the lumen, and 2 HCO_3^- ions are formed and reabsorbed **

NH_3 buffers secreted H+ in the collecting duct

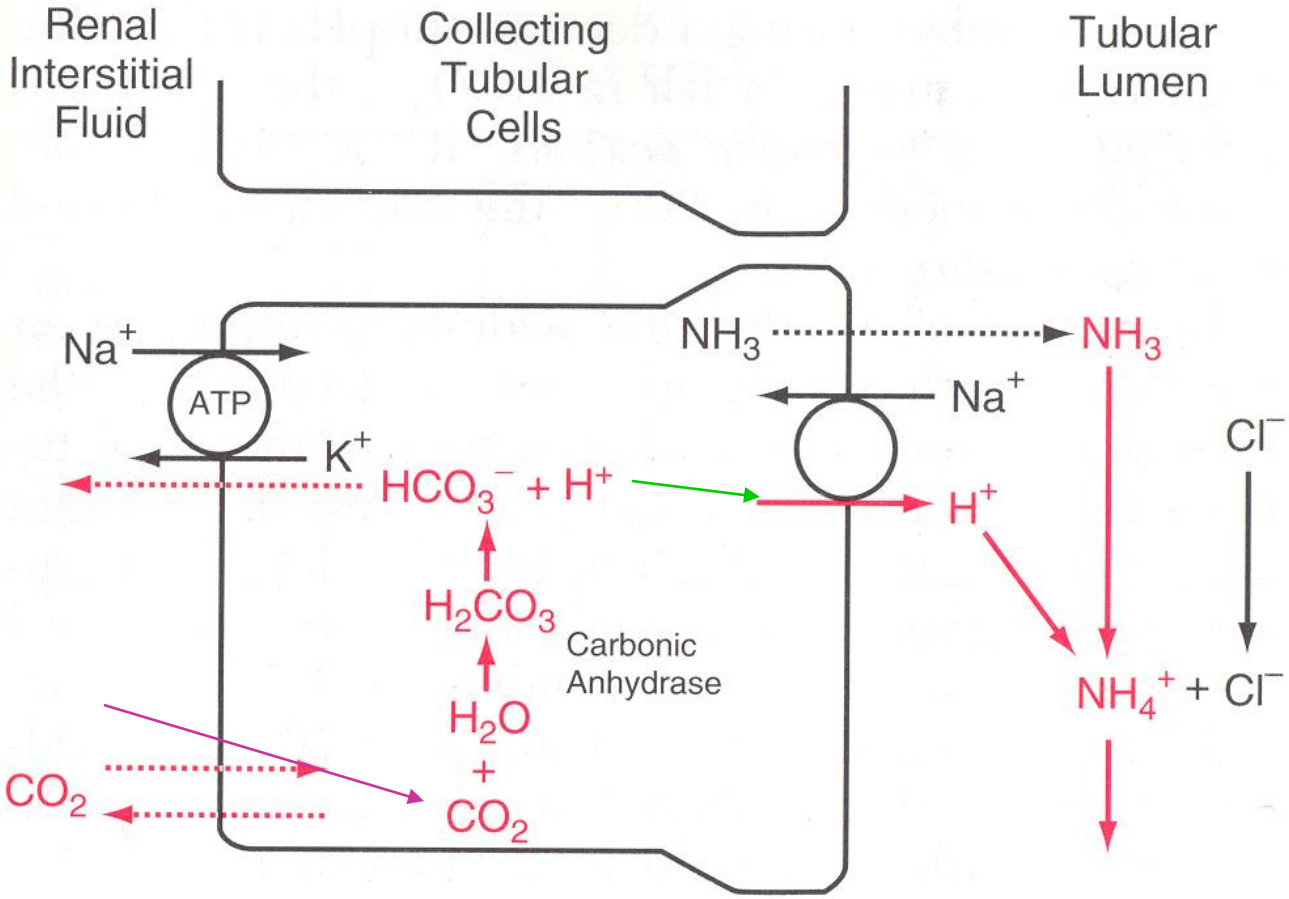


Figure 30–9. Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted hydrogen ions to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

Secreted H+ combines with NH_3 which freely diffuses into the lumen from cells to complex with H+ in the lumen to form NH_4+ which is trapped in the lumen and excreted. Again, the loss of a H^+ from the cell creates de-novo synthesis of a HCO_3^- molecule to be reabsorbed.

Disorders of A-B balance

- **Acidosis:** abnormal condition lowering arterial pH
  - before secondary changes in response to the primary etiological factor
- **Alkalosis:** abnormal condition raising arterial pH
  - before secondary changes in response to the primary etiological factor

- **Simple A-B disorders:** there is a single primary etiological acid-base disorder
- **Mixed A-B disorders:** more primary etiological disorders are present simultaneously

Acidaemia: arterial pH<7.36 (i.e. [H+]>44 nM)
Alkalaemia: arterial pH>7.44 (i.e. [H+]<36 nM)

Causes

- Respiratory
  - abnormal processes which tend to alter pH because of a primary change in **pCO_2** levels
    - acidosis
    - alkalosis
- Metabolic
  - abnormal processes which tend to alter pH because of a primary change in **$[HCO_3^-]$**
    - acidosis
    - alkalosis

Respiratory acidosis (RA)

- Primary disorder is a ***↓pH*** due to ***↑$PaCO_2$*** (>40 mmHg), i.e. hypercapnia
- Time course: - Acute (↓pH)
  - Chronic (↓pH or normalisation of pH)
    - renal compensation – retention of HCO_3^-, 3-4 days
- Causes:
  - Decreased alveolar ventilation : The defect leading to this can occur at any level in the respiratory control mechanism
  - (presence of excess CO_2 in the inspired gas)
  - (increased production of CO_2 by the body)

A rise in arterial pCO_2 is a potent stimulus to ventilation so a respiratory acidosis will rapidly correct unless some abnormal factor is maintaining the hypoventilation

Causes of Respiratory Acidosis

- Central respiratory depression & other CNS problems
  - drug depression of respiratory center (e.g. by opiates, sedatives, anaesthetics)
  - CNS trauma, infarct, haemorrhage or tumour
  - hypoventilation of obesity (e.g. Pickwick syndrome)
  - cervical cord trauma or lesions (at or above C4 level)
  - high central neural blockade
  - poliomyelitis
  - tetanus
  - cardiac arrest with cerebral hypoxia
- Nerve or muscle disorders
  - Guillain-Barre syndrome
  - Myasthenia gravis
  - muscle relaxant drugs
  - toxins e.g. organophosphates, snake venom
  - various myopathies
- Lung or chest wall defects
  - acute on COPD
  - chest trauma -contusion, haemothorax
  - pneumothorax
  - diaphragmatic paralysis
  - pulmonary oedema
  - adult respiratory distress syndrome
  - restrictive lung disease
  - aspiration
- Airway disorders
  - upper airway obstruction
  - laryngospasm
  - bronchospasm / asthma(severe)
- External factors
  - Inadequate mechanical ventilation

Rare causes of respiratory acidosis

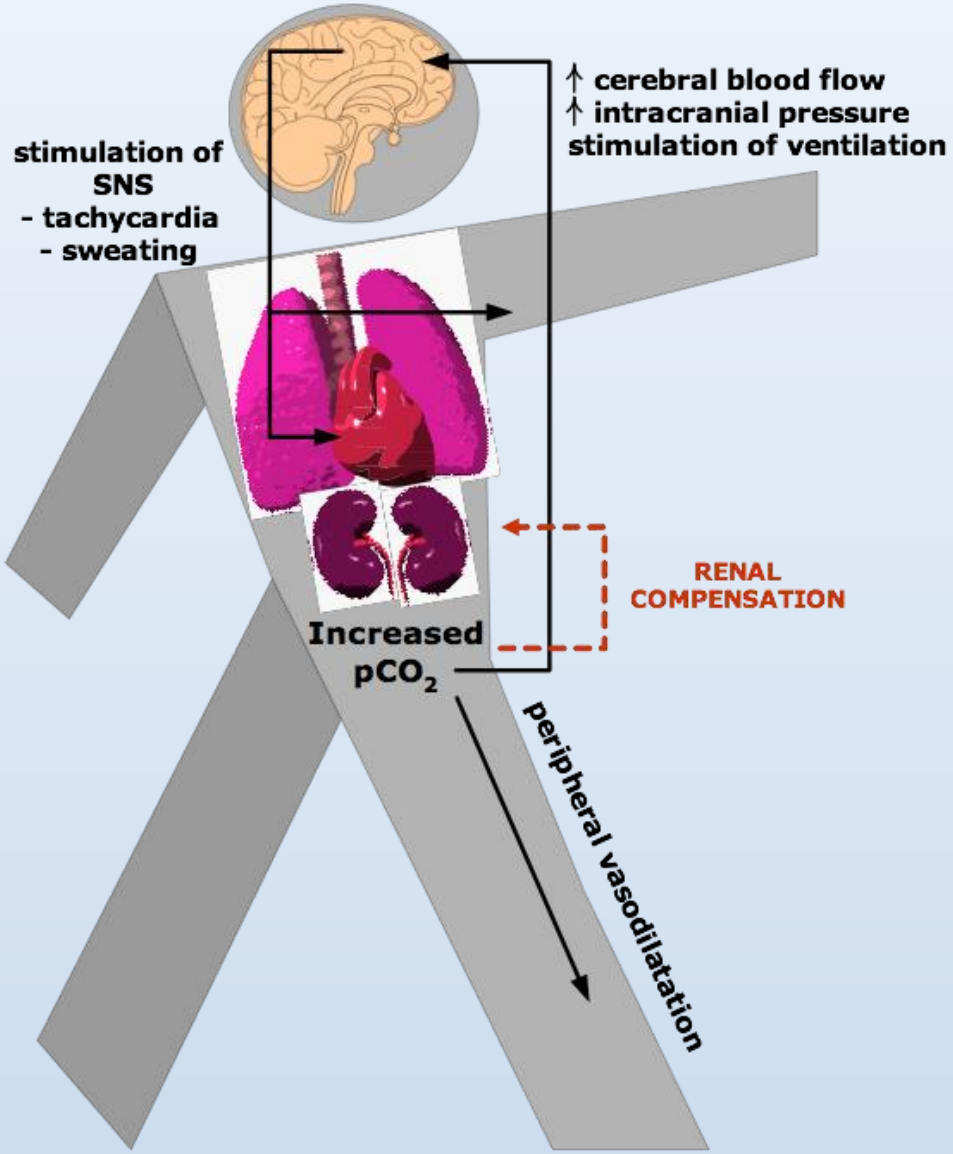
- Over-production of CO_2 in hypercatabolic disorders
  - malignant hyperthermia
  - sepsis

- Increased intake of CO_2
  - re-breathing of CO_2-containing expired gas
  - addition of CO_2 to inspired gas
  - insufflation of CO_2 into body cavity (e.g. for laparoscopic surgery)

Metabolic effects of respiratory acidosis (hypercapnia!)

- Depression of intracellular metabolism
- Cerebral effects
- Cardiovascular system

  - Extremely high hypercapnia:
    - anaesthetic effects (pCO_2>100mmHg)
    - hypoxaemia



Compensation of respiratory acidosis

- Acute RA - buffering only!
  - about 99% of this buffering occurs intracellularly
    - proteins (haemoglobin and phosphates) are the most important intravascular buffers for CO2 but their concentration is low relative to the amount of carbon dioxide requiring buffering
  - the bicarbonate system is not responsible for any buffering of a respiratory acid-base disorder - system cannot buffer itself

- Chronic RA - renal bicarbonate retention
  - takes 3 or 4 days to reach its maximum
  - $paCO_2 \rightarrow pCO_2$ in proximal tubular cells $\rightarrow$ H+ secretion into the lumen:
    - HCO_3 production which crosses the basolateral membrane and enters the circulation (so plasma $[HCO_3]$ increases)
    - Na^+ reabsorption in exchange for H^+
    - NH_3 production to 'buffer' the H^+ in the tubular lumen (so urinary excretion of NH_4Cl increases)

Respiratory acidosis	< 7.35	Compensatory increase	Primary increase	**Acute:** 1–2 mmol/L increase in HCO_3^- for every 10-mm Hg increase in P_{CO_2} **Chronic:** 3–4 mmol/L increase in HCO_3^- for every 10-mm Hg increase in P_{CO_2}

Treatment of respiratory acidosis

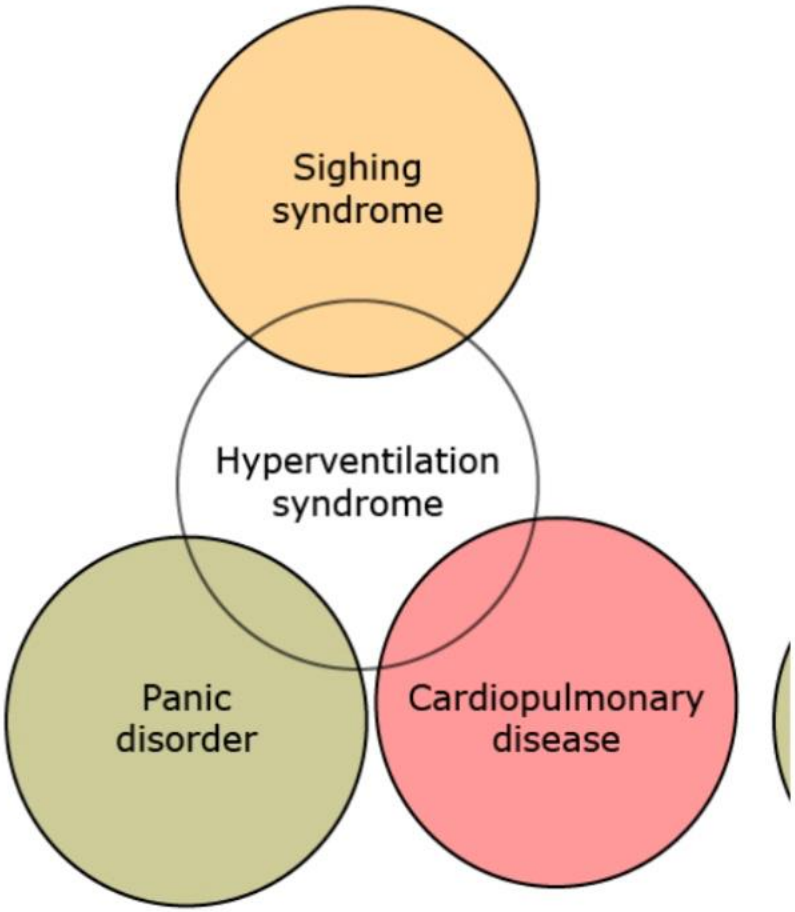
- Treat the primary cause if this is possible
- Rapid fall in pCO_2 especially in chronic RA, can cause
  - severe hypotension
  - Post hypercapnic alkalosis'

Respiratory alkalosis

- Primary disorder is a***pH*** due to ↓***$PaCO_2$*** (<35 mmHg), i.e. hypocapnia
- Time course:
  - acute (pH)
  - chronic (pH or normalisation of pH)
    - renal compensation – 3-4 days
- Causes : CNS disease (brain tumor)
  Toxins (Salicylates)
  High altitude
  pneumonia, pulmonary emboli
  sepsis
  liver cirrhosis

Respiratory alkalosis	> 7.45	Compensatory decrease	Primary decrease	**Acute:** 1–2 mmol/L decrease in HCO_3^- for every 10-mm Hg decrease in P_{CO_2} **Chronic:** 4–5 mmol/L decrease in HCO_3^- for every 10-mm Hg decrease in P_{CO_2}

Hyperventilation syndrome and overlapping disorders



Hyperventilation and overlapping clinical pictures. In the assessment of the patient presenting with hyperventilation, one needs to consider the potential contributions of behavioral disorders and seemingly inappropriate dyspnea in the presence of known cardiopulmonary disease. The size of the circles is not meant to imply relative prevalence of the conditions.

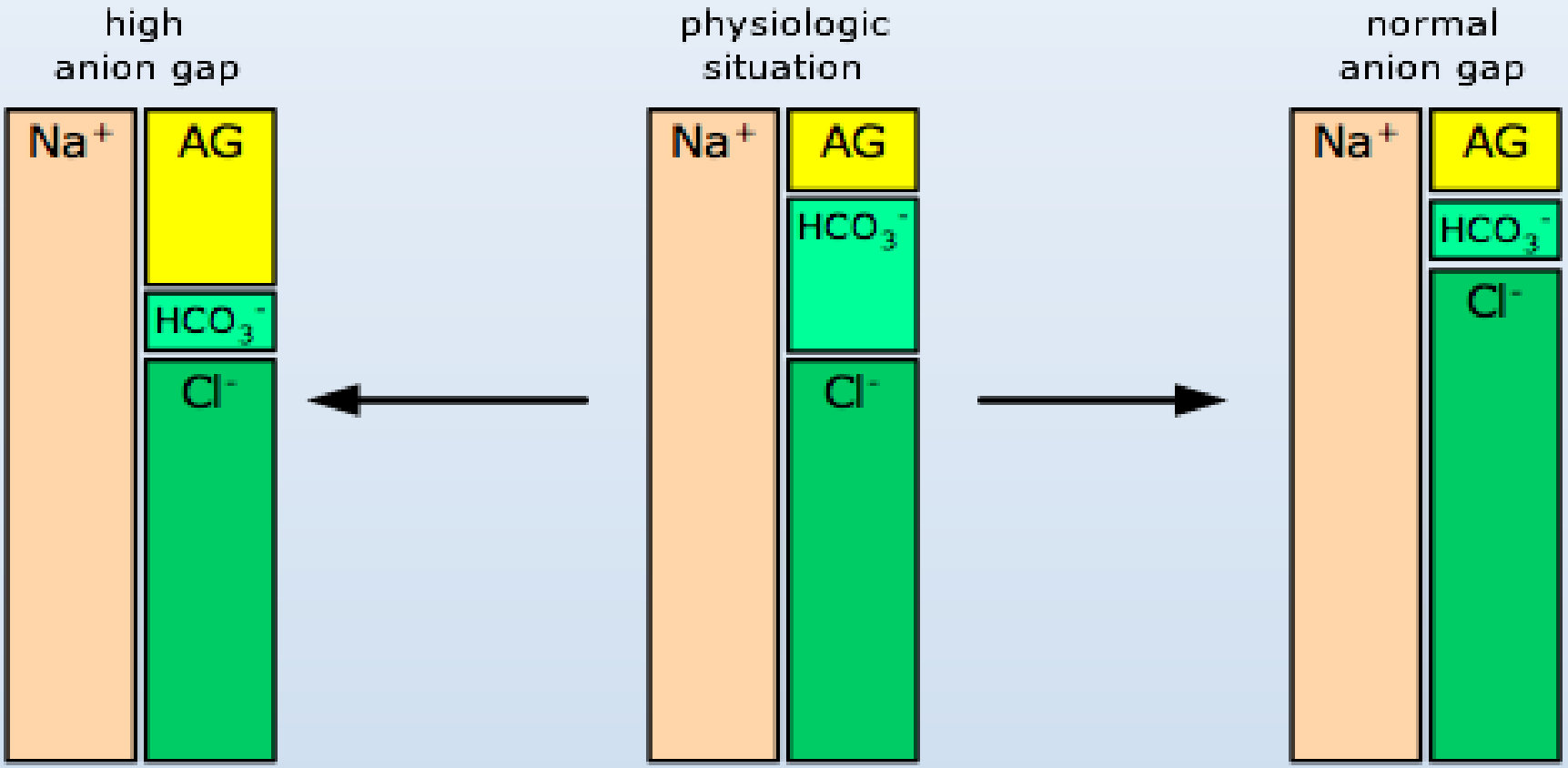
Metabolic acidosis

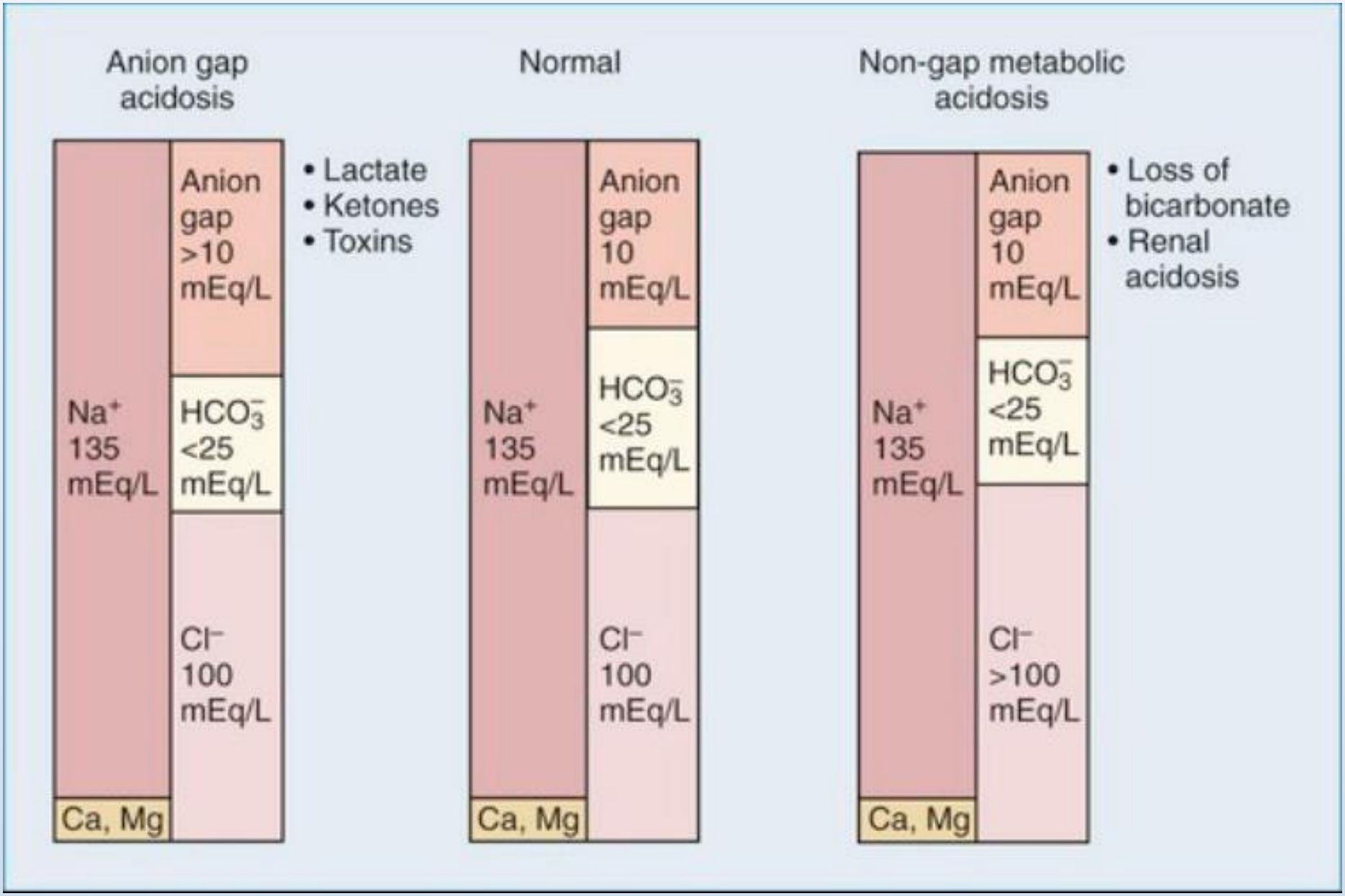
- Primary disorder is a ***↓pH*** due to ***↓HCO_3^-***:
  - ↑ fixed $[H^+]$ = high anion gap
  - loss or ↓ reabsorption of HCO_3^- = normal anion gap

$$AG = [Na^+] - [Cl^-] - [HCO_3^-]$$

  - The effect of low albumin can be accounted for by adjusting the normal range for the anion gap 2.5 mEq/L for every 1 g/dL fall in albumin.

Causes of Metabolic Acidosis

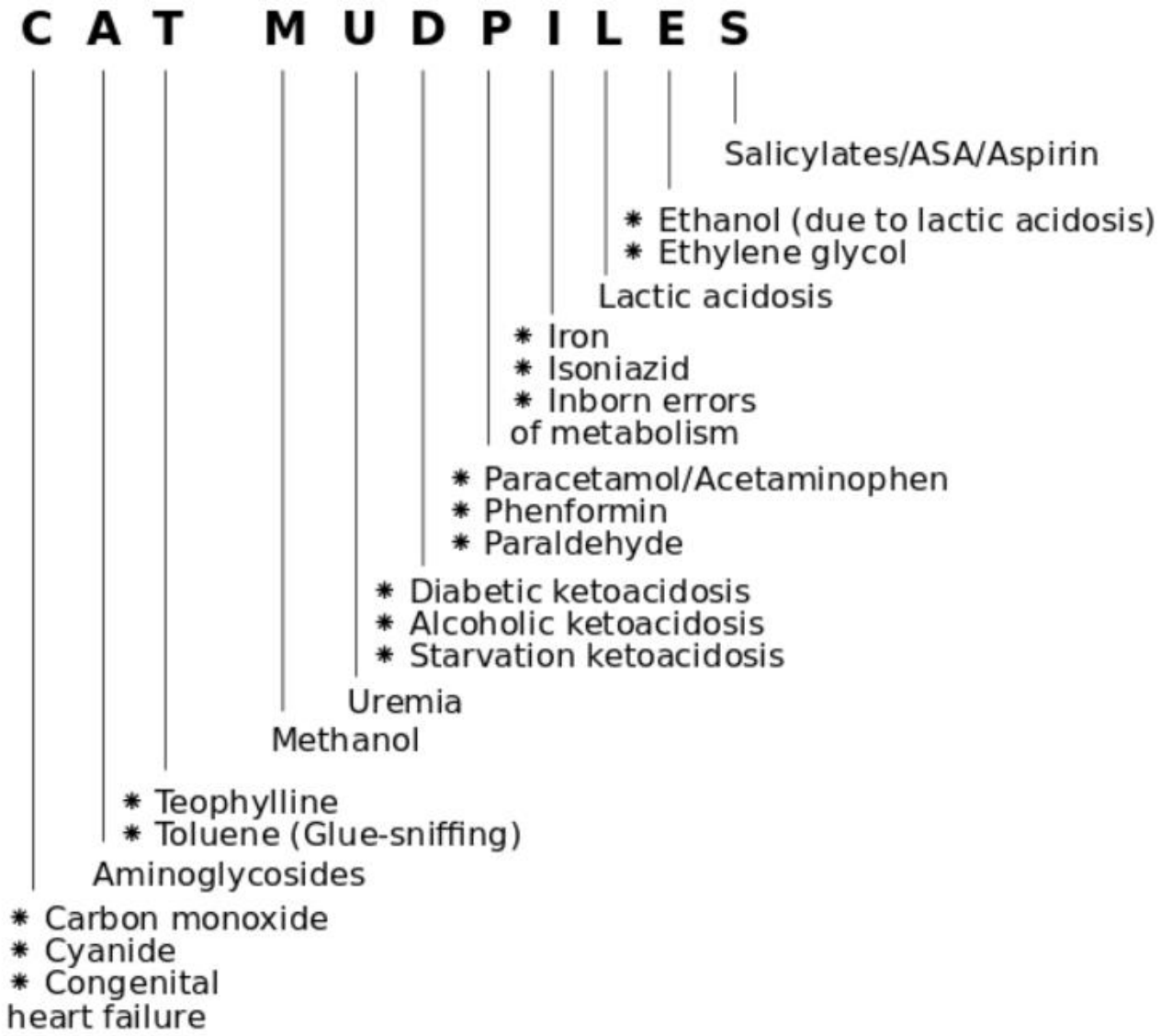



Anion gap acidosis
Anion gap >10 mEq/L
HCO_3^- <25 mEq/L
Na^+ 135 mEq/L
Cl^- 100 mEq/L
Ca, Mg
• Lactate
• Ketones
• Toxins
Normal
Anion gap 10 mEq/L
HCO_3^- <25 mEq/L
Na^+ 135 mEq/L
Cl^- 100 mEq/L
Ca, Mg
Non-gap metabolic acidosis
Anion gap 10 mEq/L
HCO_3^- <25 mEq/L
Na^+ 135 mEq/L
Cl^- >100 mEq/L
Ca, Mg
• Loss of bicarbonate
• Renal acidosis

Major causes of metabolic acidosis according to mechanism and anion gap

Mechanism of acidosis	Increased AG	Normal AG
Increased acid production	Lactic acidosis	
	Ketoacidosis	
	Diabetes mellitus	
	Starvation	
	Alcohol-associated	
	Ingestions	
	Methanol	
	Ethylene glycol	
	Aspirin	
	Toluene (if early or if kidney function is impaired)	Toluene ingestion (if late and if renal function is preserved - due to excretion of sodium and potassium hippurate in the urine)
	Diethylene glycol	
	Propylene glycol	
	D-lactic acidosis	
	Pyroglutamic acid (5-oxoproline)	
Loss of bicarbonate or bicarbonate precursors		Diarrhea or other intestinal losses (eg, tube drainage)
		Type 2 (proximal) renal tubular acidosis (RTA)
		Posttreatment of ketoacidosis
		Carbonic anhydrase inhibitors
		Ureteral diversion (eg, ileal loop)
Decreased renal acid excretion	Chronic kidney disease	Chronic kidney disease and tubular dysfunction (but relatively preserved glomerular filtration rate)
		Type 1 (distal) RTA
		Type 4 RTA (hypoaldosteronism)

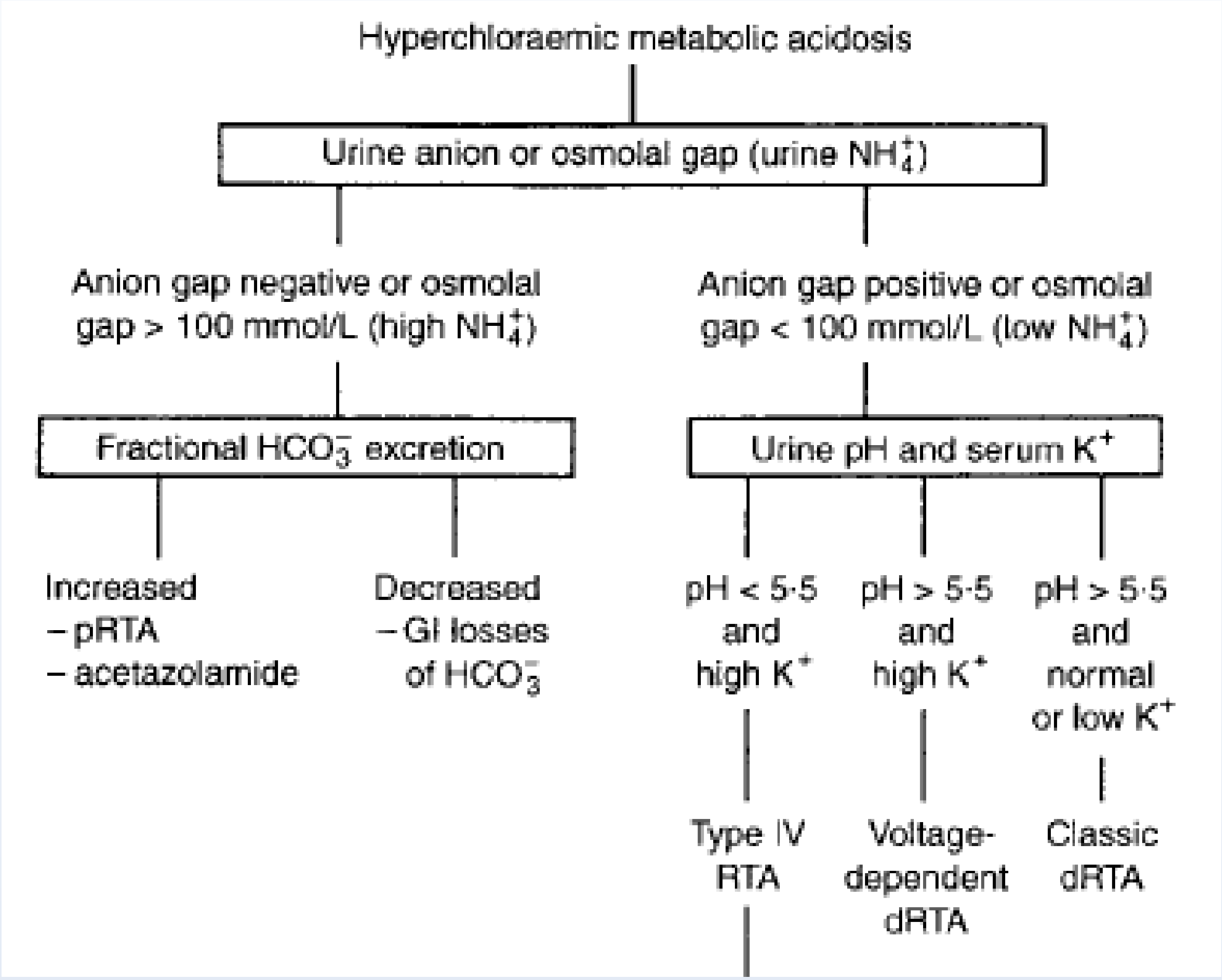
Causes of high anion-gap metabolic acidosis



Non anion gap metabolic acidosis Causes

Non-Anion Gap acidosis (Hyperchloremic Metabolic acidosis)

- **GI HCO3 loss**
  - Diarrhoea
  - Ureterosigmoidostomy, , GI fistula, villous adenoma, ileal conduit
- **Renal acidosis**
  - Hypokalemia – RTA 2/ RTA 1
  - Hyperkalemia – RTA 4/ MC deficiency/ MC resistance
  - Tubulointerstitial disease


Hyperchloraemic metabolic acidosis
Urine anion or osmolal gap (urine NH_4^+)
Anion gap negative or osmolal gap > 100 mmol/L (high NH_4^+)
Anion gap positive or osmolal gap < 100 mmol/L (low NH_4^+)
Fractional HCO_3^- excretion
Urine pH and serum K^+
Increased
– pRTA
– acetazolamide
Decreased
– GI losses of HCO_3^-
pH < 5·5 and high K^+
pH > 5·5 and high K^+
pH > 5·5 and normal or low K^+
Type IV RTA
Voltage-dependent dRTA
Classic dRTA

Non-Anion Gap Metabolic Acidosis

GI. BICARBONATE LOSS

- NORMAL AG, HYPERCHLOREMIC
- CAUSES
  - DIARRHEA
  - EXTERNAL FISTULA
  - URETEROSIGMOIDOSTOMY OR ILEAL LOOP CONDUIT

RENAL BICARBONATE LOSS

- TYPE I RTA (DISTAL, CLASSICAL)
  - PROTON SECRETION DEFECT
- TYPE II RTA (PROXIMAL, FANCONOI)
  - BICARBONATE REABSORPTION DEFECT
- TYPE IV RTA (HYPERKALEMIC)
  - HYPORENINEMIC HYPOALDOSTERONISM

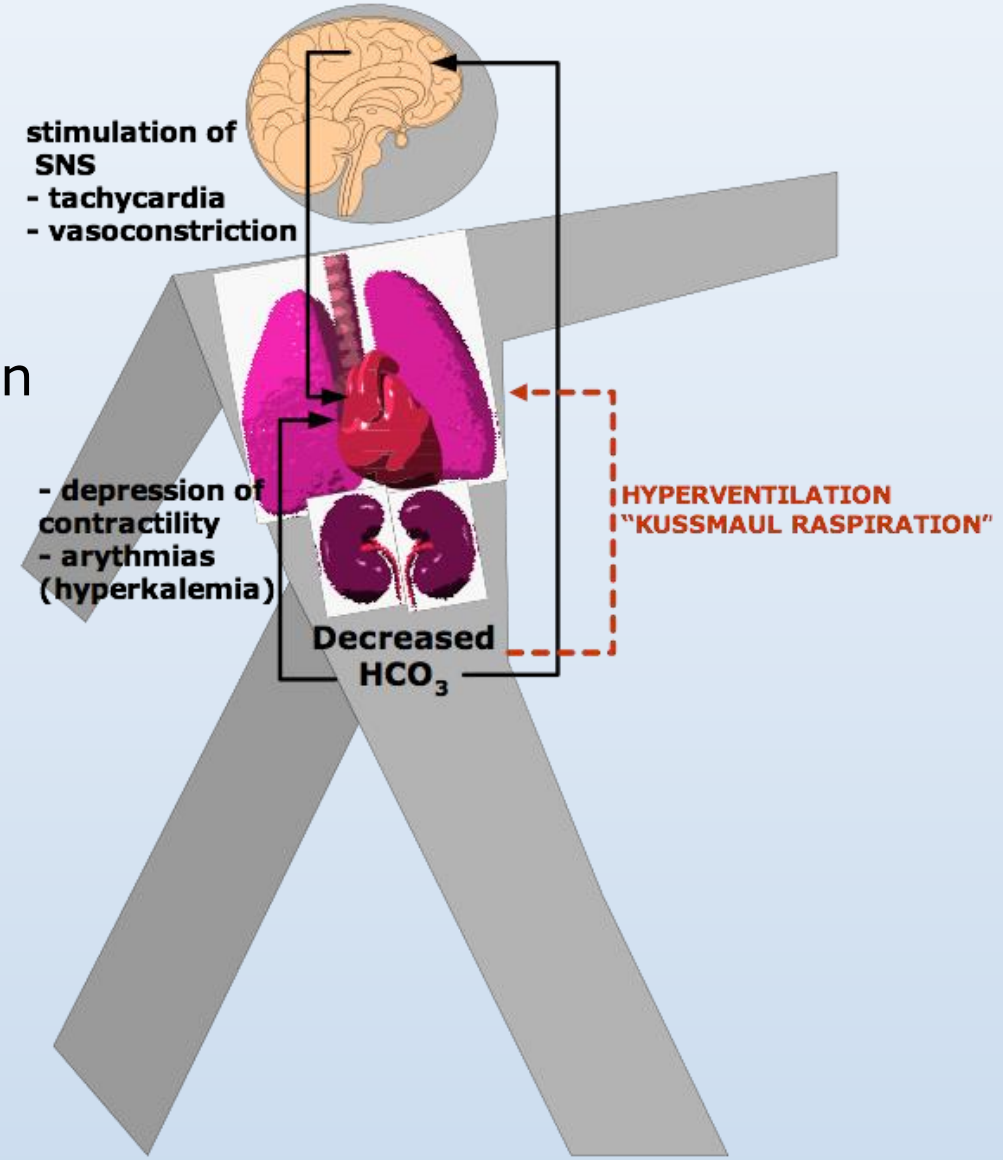
Metabolic acidosis	< 7.35	Primary decrease	Compensatory decrease	1.2-mm Hg decrease in Pco_2 for every 1-mmol/L decrease in HCO_3^- ***or*** $Pco_2 = (1.5 \times HCO_3^-) + 8 (\pm 2)$ ***or*** $Pco_2 = HCO_3^- + 15$ *or* Pco_2 = last 2 digits of pH × 100

Decreased Anion Gap

- Hypoalbuminemia
- Hypercalcemia
- Hypermagnesemia
- Lithium intoxication
- Hypergammaglobulinemia
- Bromide or iodide intoxication

Metabolic Acidosis - Metabolic effects

- Respiratory
  - hyperventilation
  - shift of haemoglobin dissociation curve to the right
  - decreased 2,3 DPG levels in red cells (shifting the ODC back to the left)
- Cardiovascular
- Others
  - increased bone resorption (chronic acidosis only)
  - shift of K^+ out of cells causing hyperkalaemia



Cardiovascular	Impaired cardiac contractility Arteriolar dilation Venoconstriction Centralization of blood volume Increased pulmonary vascular resistance Decreased cardiac output Decreased systemic BP Decreased hepatorenal blood flow Decreased threshold for cardiac arrhythmias Attenuation of responsiveness to catecholamines	Arteriolar constriction Reduced coronary blood flow Reduced anginal threshold Decreased threshold for cardiac arrhythmias

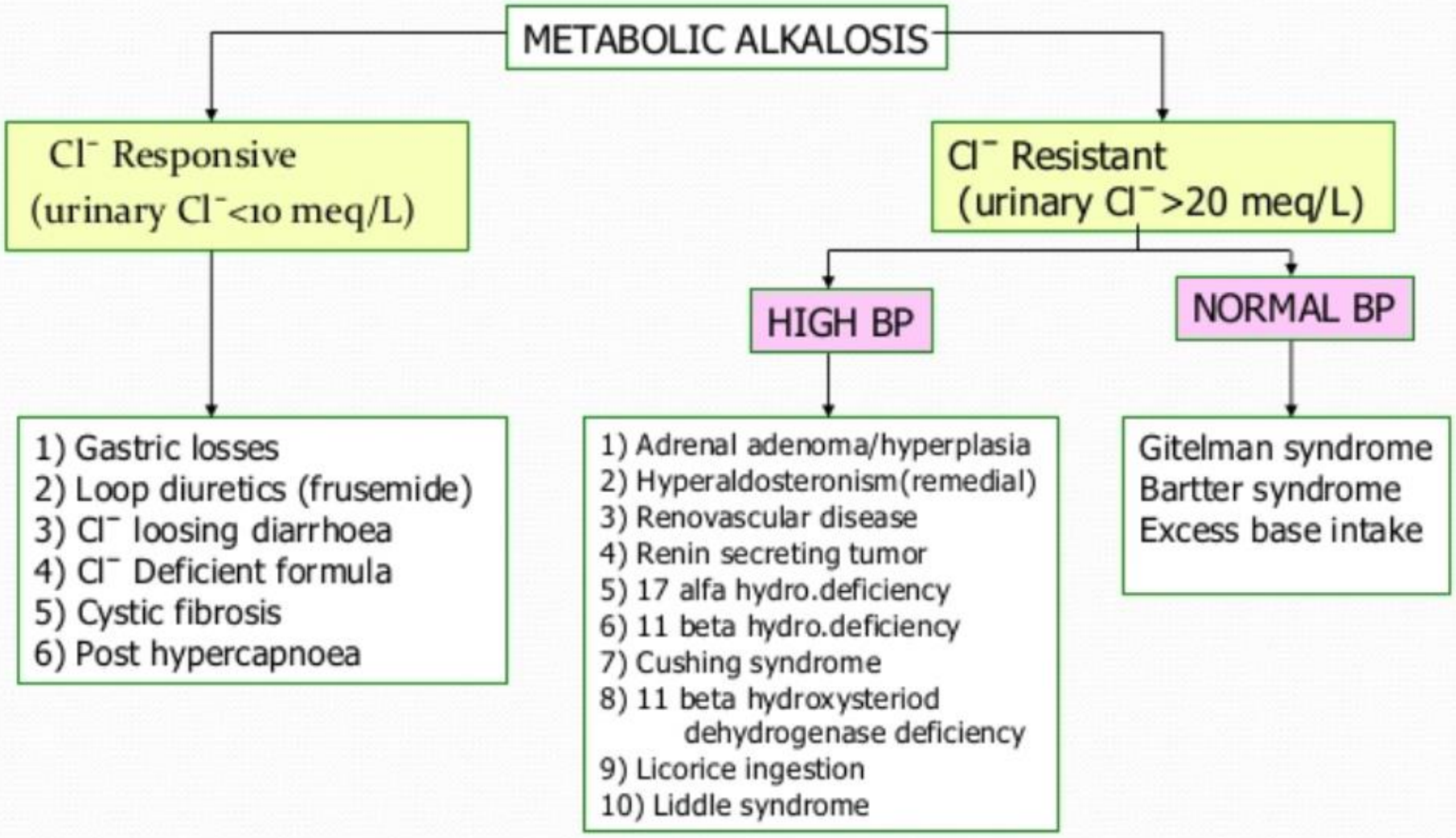
Metabolic	Insulin resistance Inhibition of anaerobic glycolysis Reduction in ATP synthesis Hyperkalemia Protein degradation Bone demineralization (chronic)	Stimulation of anaerobic glycolysis Formation of organic acids Decreased oxyhemoglobin dissociation Decreased ionized Ca Hypokalemia Hypomagnesemia Hypophosphatemia
Neurologic	Inhibition of metabolism and cell-volume regulation Obtundation and coma	Tetany Seizures Lethargy Delirium Stupor
Respiratory	Compensatory hyperventilation with possible respiratory muscle fatigue	Compensatory hypoventilation with hypercapnia and hypoxemia

Metabolic alkalosis

Primary disorder is a↑pH due to↑HCO_3^-
Causes of metabolic alkalosis

- Volume - depleted type:
  - Gastric acid loss
    - Vomiting
    - NGT suction
  - Renal chloride loss
    - Diuretics
    - Hypercapnia correction
- Volume - repleted type:
  - Mineralocorticoid excess
    - Hyperaldosteronism
    - Bartter's syndrome
    - Cushing's syndrome
    - Licorice excess
  - Profound potassium depletion

DIAGNOSIS


METABOLIC ALKALOSIS
Cl⁻ Responsive
(urinary Cl⁻<10 meq/L)
Cl⁻ Resistant
(urinary Cl⁻>20 meq/L)
HIGH BP
NORMAL BP
1) Gastric losses
2) Loop diuretics (frusemide)
3) Cl⁻ loosing diarrhoea
4) Cl⁻ Deficient formula
5) Cystic fibrosis
6) Post hypercapnoea
1) Adrenal adenoma/hyperplasia
2) Hyperaldosteronism(remedial)
3) Renovascular disease
4) Renin secreting tumor
5) 17 alfa hydro.deficiency
6) 11 beta hydro.deficiency
7) Cushing syndrome
8) 11 beta hydroxysteriod dehydrogenase deficiency
9) Licorice ingestion
10) Liddle syndrome
Gitelman syndrome
Bartter syndrome
Excess base intake

Effects of Metabolic Alkalosis

- Decreased serum potassium
- Decreased serum ionized calcium
- Dysrhythmias
- Hypoventilation / hypoxemia
- Increased bronchial tone / atelectasis
- Left shift of the Oxygen curve

- The difference between the patient's anion gap and the normal anion gap is termed the delta gap

- considered an HCO_3^- equivalent, because for every unit Rise in the anion gap, the HCO_3^- should lower by 1

- The delta gap is added to the measured HCO_3^- , the result should be in the normal range for HCO_3^-; elevation indicates the additional presence of a metabolic alkalosis and lower Hco3 indicates presence metabolic acidosis

MIXED ACID-BASE DISORDERS

- **Metabolic and respiratory acidosis (serious)**
- **Metabolic and respiratory alkalosis (serious)**
- **Metabolic acidosis & respiratory alkalosis**
- **Metabolic alkalosis & respiratory acidosis**
- **Metabolic acidosis & alkalosis + resp. disorder**

Thank you