Renal H+ secretion and HCO3 reabsorption

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Overview

- Volatile and Nonvolatile acids
- Reabsoprption of bicarbonate
- Secretion of H^+
- Buffer systems

Introduction

- The key parameter involved in acid–base regulation is the concentration of H+ in the ECF.

$$pH = pK_a + \log \frac{[HCO_3^-]}{[CO_2]}$$

- The physiological set point for this parameter is 40nmol/L, usually expressed as the pH, which is normally 7.40.

- pH is tightly regulated in the range 7.38–7.42.

Votatile acid

- Two forms of acid are generated as a result of normal metabolic processes.

- Oxidative metabolism produces a large amount of CO2 daily- 'volatile acid' is excreted through the lungs.

- Carbon dioxide effectively acts as an acid in body fluids because of the following reactions:

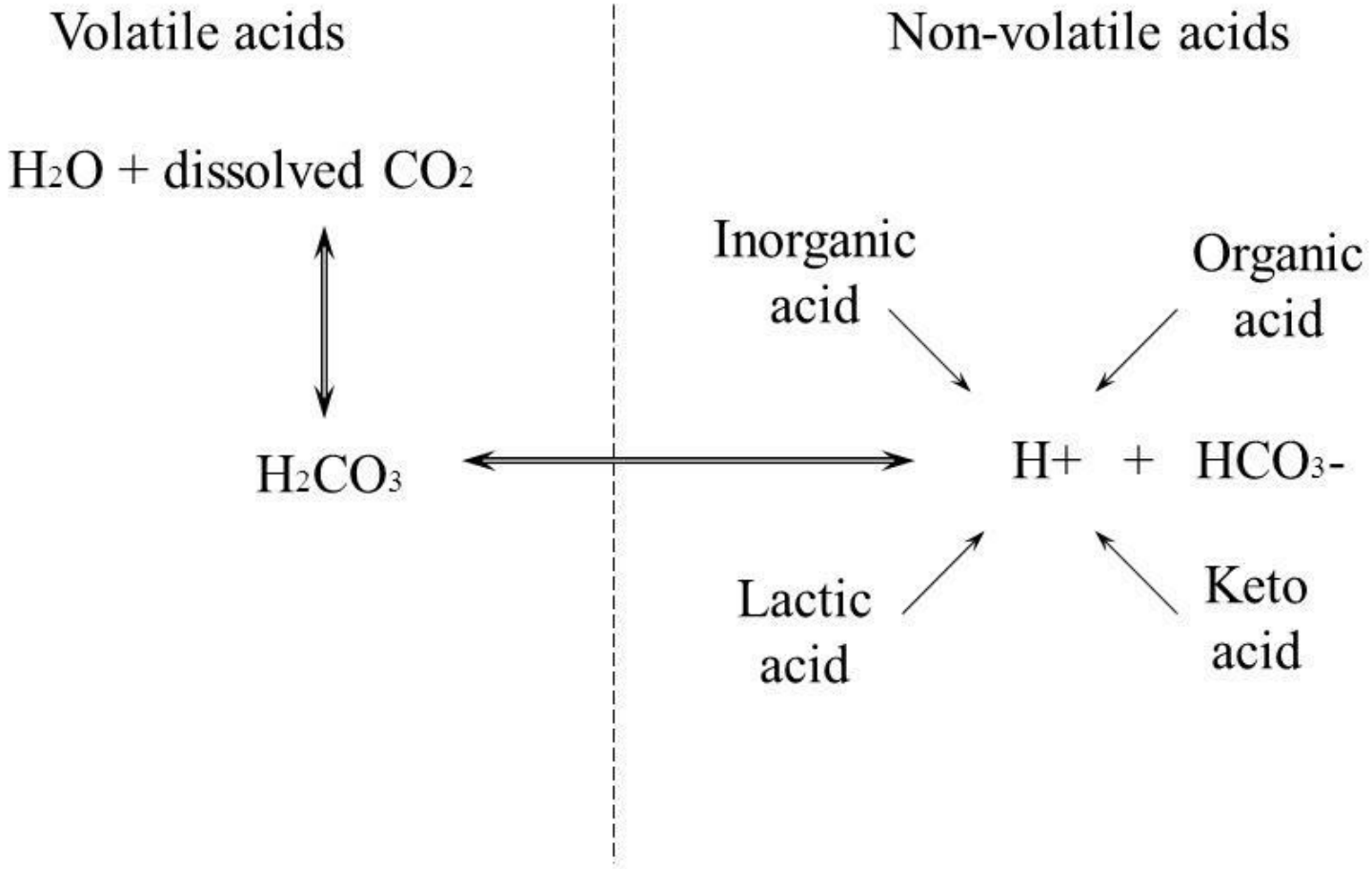
$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

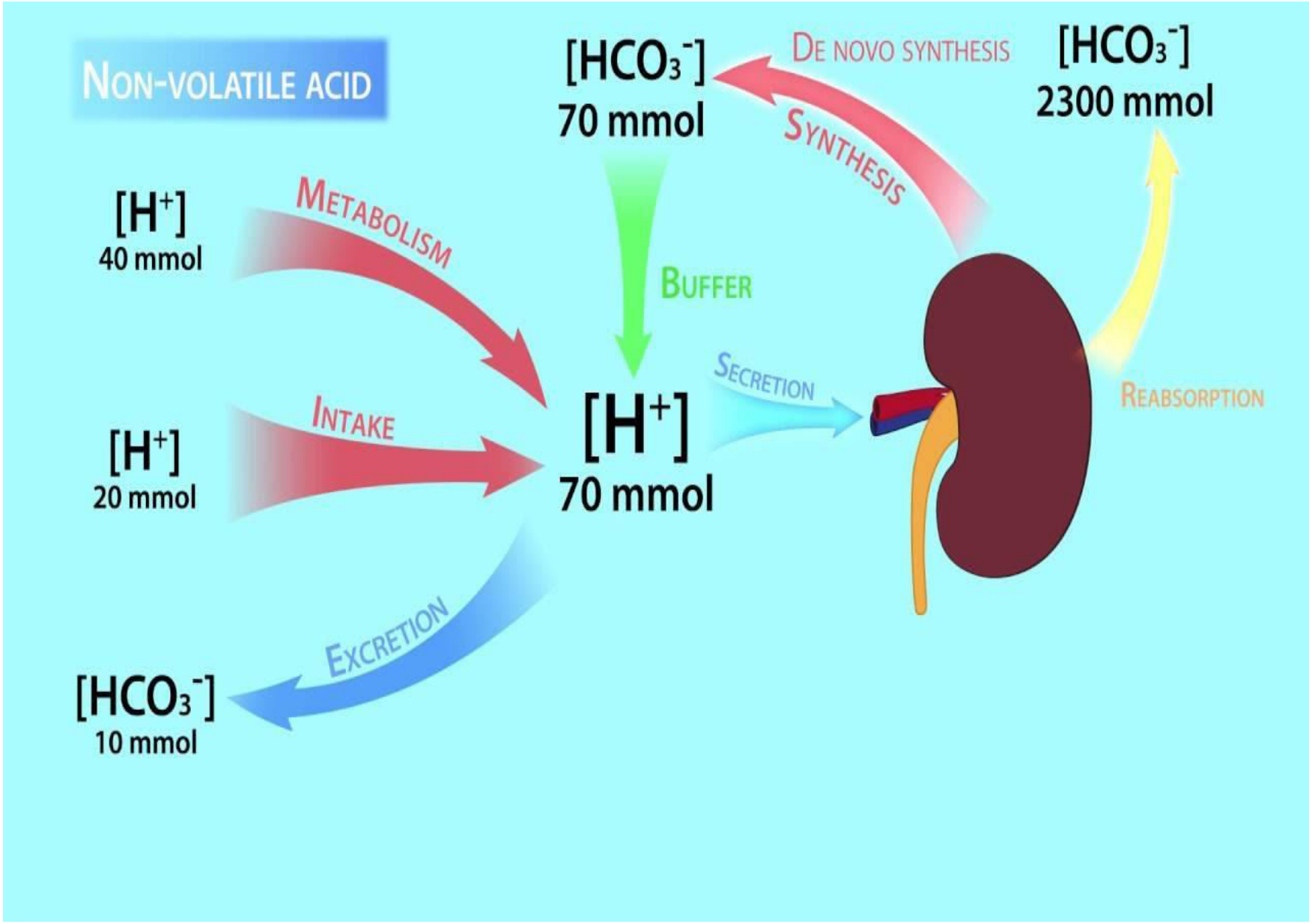
Non volatile acid

- ‘non-volatile acid’, results from the metabolism of dietary protein

- Resulting in the accumulation of 70mmol of acid per day in an average adult on a typical western meatcontaining diet.

Sources of blood acids




NON-VOLATILE ACID
[HCO3-]
70 mmol
DE NOVO SYNTHESIS
[HCO3-]
2300 mmol
SYNTHESIS
[H+]
40 mmol
METABOLISM
BUFFER
SECRETION
INTAKE
[H+]
20 mmol
[H+]
70 mmol
REABSORPTION
EXCRETION
[HCO3-]
10 mmol

How to maintain blood pH with these volatile acids?

Buffer systems in Kidney

- Bicarbonate
- Phophate
- Amonia

- Given that bicarbonate buffer is freely filtered at the glomerulus and that there is a daily load of non-volatile acid to be excreted into the urine, there must be two components to the nephron's task:

- reabsorption of filtered bicarbonate

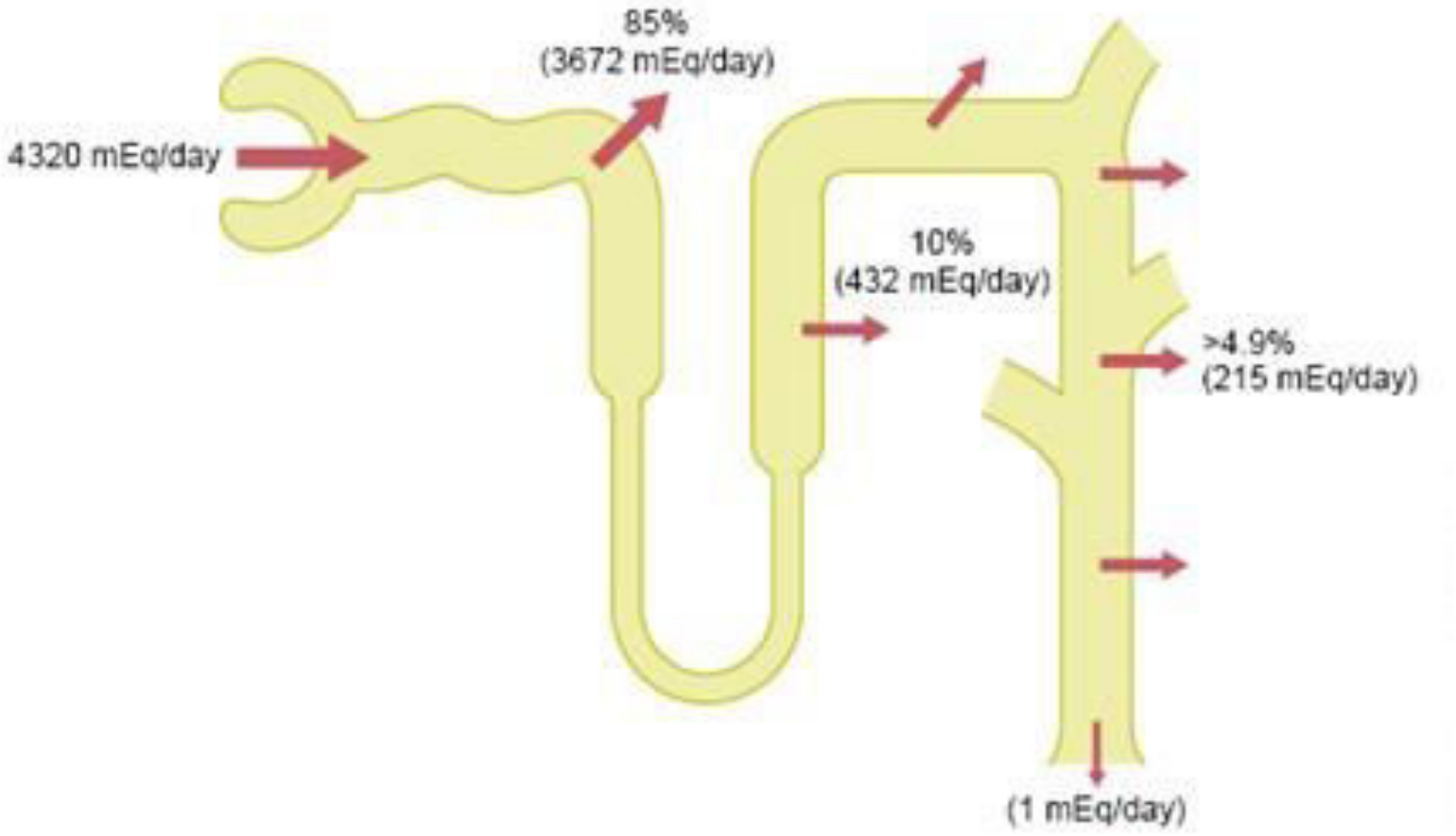
  and

- addition of net acid to the tubular fluid.

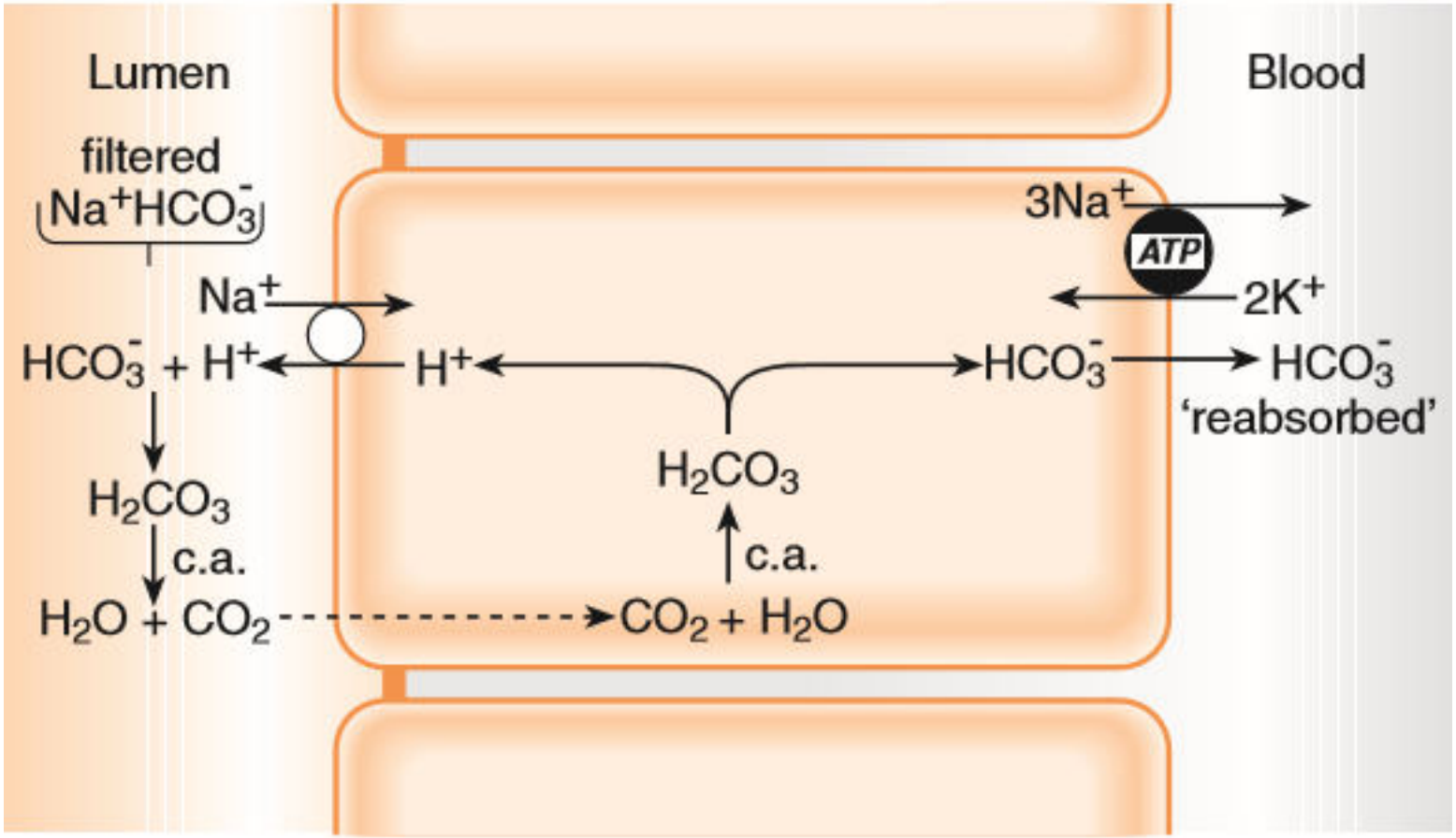
Bicarbonate reabsorption/H^+secretion in PCT

- Bicarbonate is the principal physiological buffer in the plasma
- It is freely filtered at the glomerulus.
- Bicarbonate excretion is essentially zero under normal conditions
- Extensive and efficient reabsorption of bicarbonate principally in the proximal tubule

Bicarbonate reabsorption



Bicarbonate reabsoption in PCT



Bicarbonate reabsoption in PCT

- Filtered sodium bicarbonate passing through the proximal tubule is effectively reabsorbed

- Bicarbonate added to the plasma in a given turn of the cycle is not the same one appearing in the lumen with sodium.

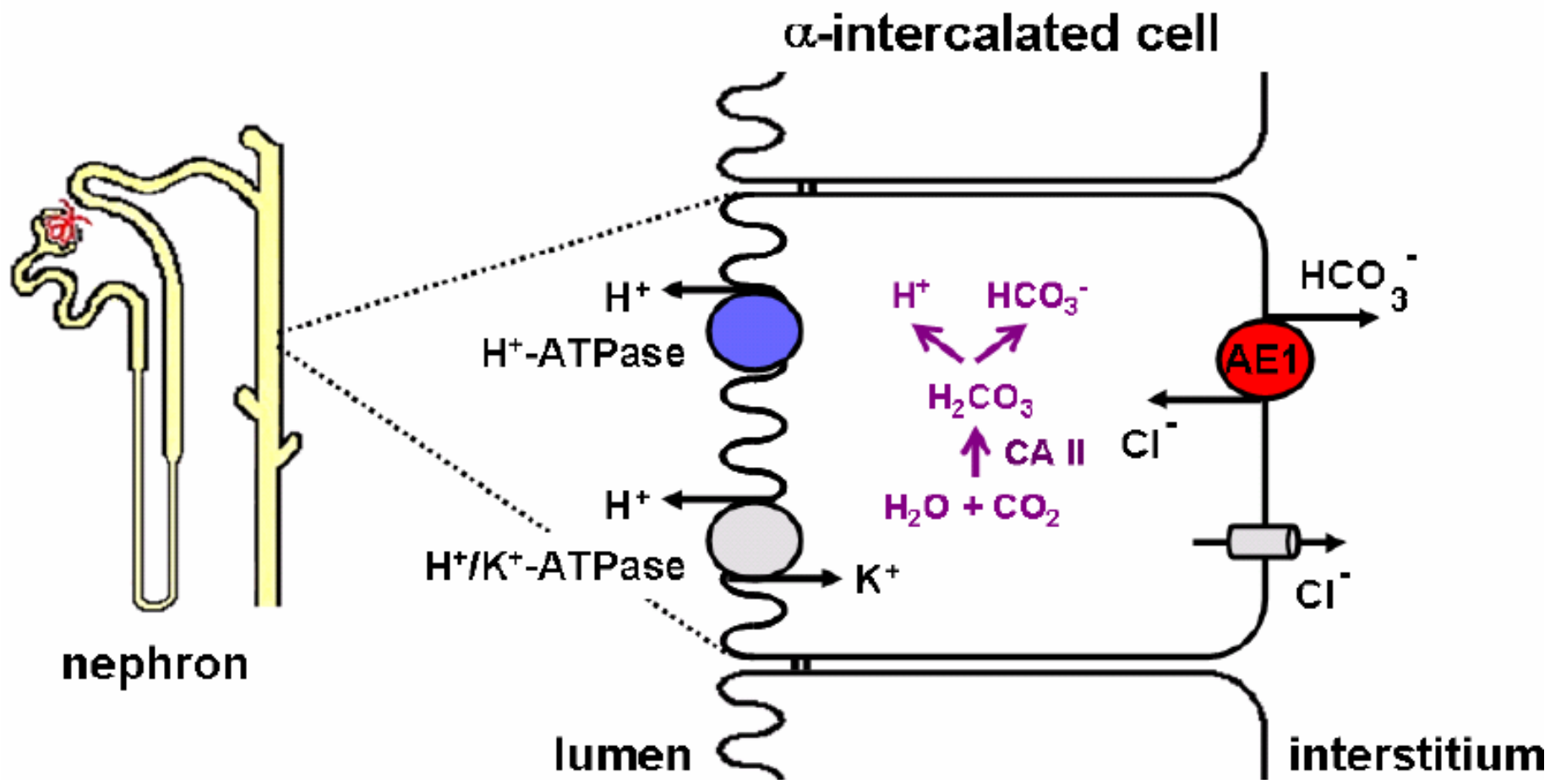
- Accounts for reabsorption of some 85% of filtered bicarbonate

- Generates a low gradient of hydrogen ion concentration across the epithelium, with the luminal pH falling only slightly from 7.4 at the glomerulus to around 7.0 at the end of the proximal tubule

H^+ sectretion in distal nephron

- Relatively independent of Na+ in tubular lumen
- I cells secrete acid
- H+ secreted by ATP - driven proton pump (aldosterone acts on it) and H+-K+ATP ase
- Anion exchanger 1 in basolateral membrane will transport HCO3 to interstitial fliud

H^+ sectretion in distal nephron



Net acid excretion

- Under circumstances requiring removal of net acid from the body, the tubules must still carry out two more steps.

- Secrete further acid into the tubular lumen beyond that needed to reabsorb all filtered bicarbonate.

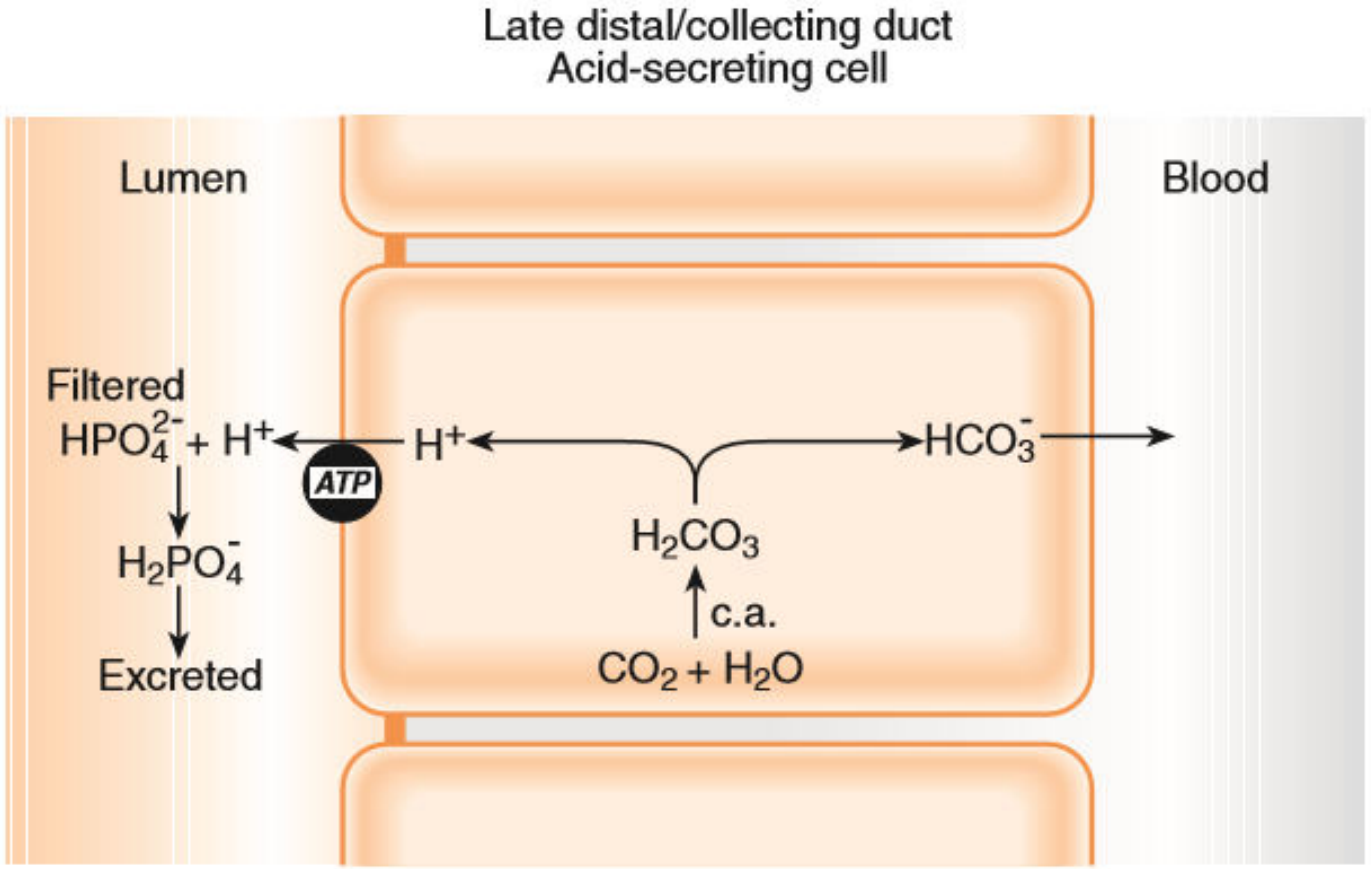
- Provide a buffer in the tubular fluid to assist in the removal of this acid.

These two requirements are fulfilled in more distal nephron segments.

Buffer systems in distal part of kidney

- Phophate
- Amonia

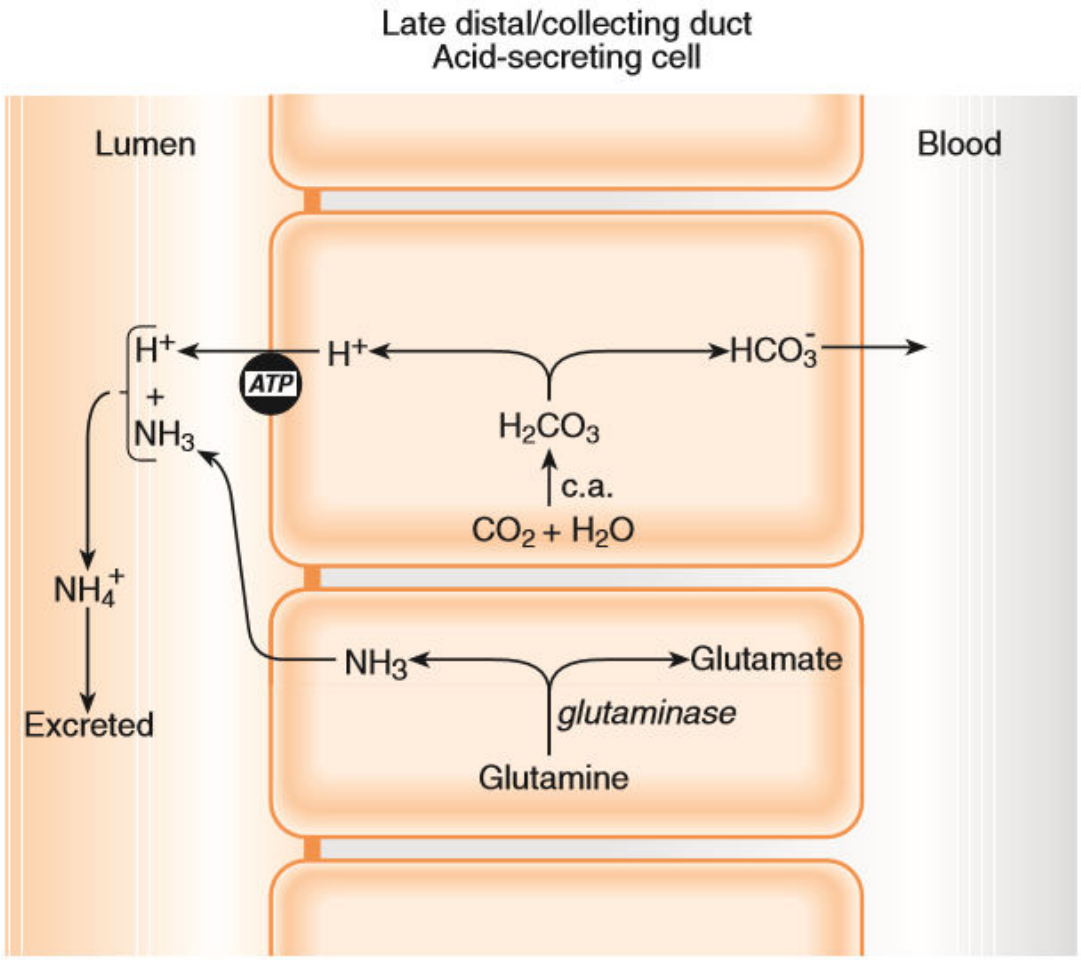
Phosphate buffer system



Phosphate buffer system

- Constant amount of Phophate filtered -1.5 mEq/L
- Occurs more in distal tubules and CT
- This reaction has limited capacity (removing up to 30mmol of H+/day)
- Tends to proceed as the urine pH falls along the distal nephron segments, typically from 7 down to 6 and below pK (acid dissociation constant) of this buffer system being 6.8.
- This form of excreted H+ is sometimes called ‘titratable acid’ as it can be quantitated by backtitrating a specimen of urine.

Amonia buffer system



Amonia buffer system

- Constitutes removal of an unwanted H+ from the body, with restoration of a ‘new’ bicarbonate molecule to the ECF.

- The importance of this mechanism for acid excretion is that it is linked to an abundant and regulated source of buffer production (NH3) of essentially unlimited capacity.

- Thus, under conditions of acid build-up (especially chronic acidosis), NH3 synthesis is stimulated and acid excretion (as ammonium) is greatly increased, allowing systemic acid–base balance to be maintained.

pH along the Nephron

- Despite the action of NH3 to buffer the build-up of free acid in the late segments of the nephron, the pH of the tubular fluid does fall along the collecting duct system, resulting in final urinary pH as low as 4.5.

- This occurs both because the distal nephron is relatively impermeable to H+ and because there is no carbonic anhydrase in the luminal compartment in these tubular segments.

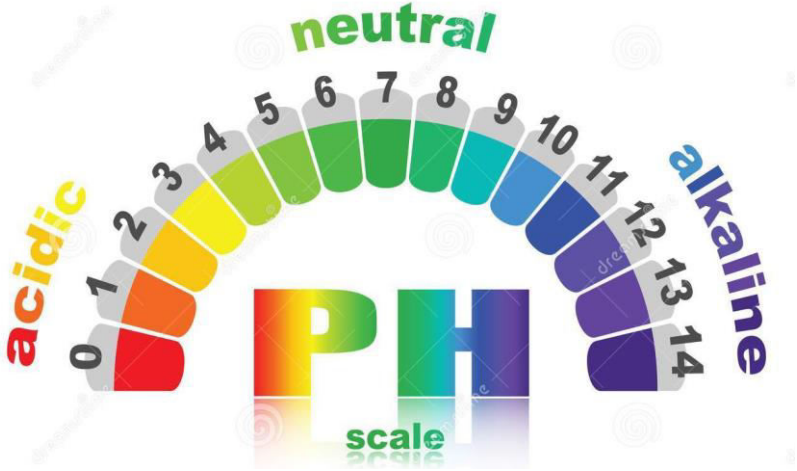
- This means that the dehydration of carbonic acid formed in the lumen is slow, allowing H+ to accumulate.

Summary

- Under conditions of normal dietary protein consumption, a slightly alkaline plasma pH of 7.40 is maintained despite the generation of about 70mmol of hydrogen ion per day.
- The kidney's role in maintaining this pH homeostasis is achieved by generating an acidic urine in which the net daily excess of acid can be removed. It does this in the following ways.

- Reabsorbing all bicarbonate buffer filtered into the urine.
- Secreting H+ for excretion with filtered buffers such as phosphate.
- Secreting H+ for excretion with the manufactured buffer ammonia

Acid Base Balance



Introduction

- Acid-base homeostasis critically affects tissue and organ performance

- Both acidosis and alkalosis can have severe and life threatening consequences

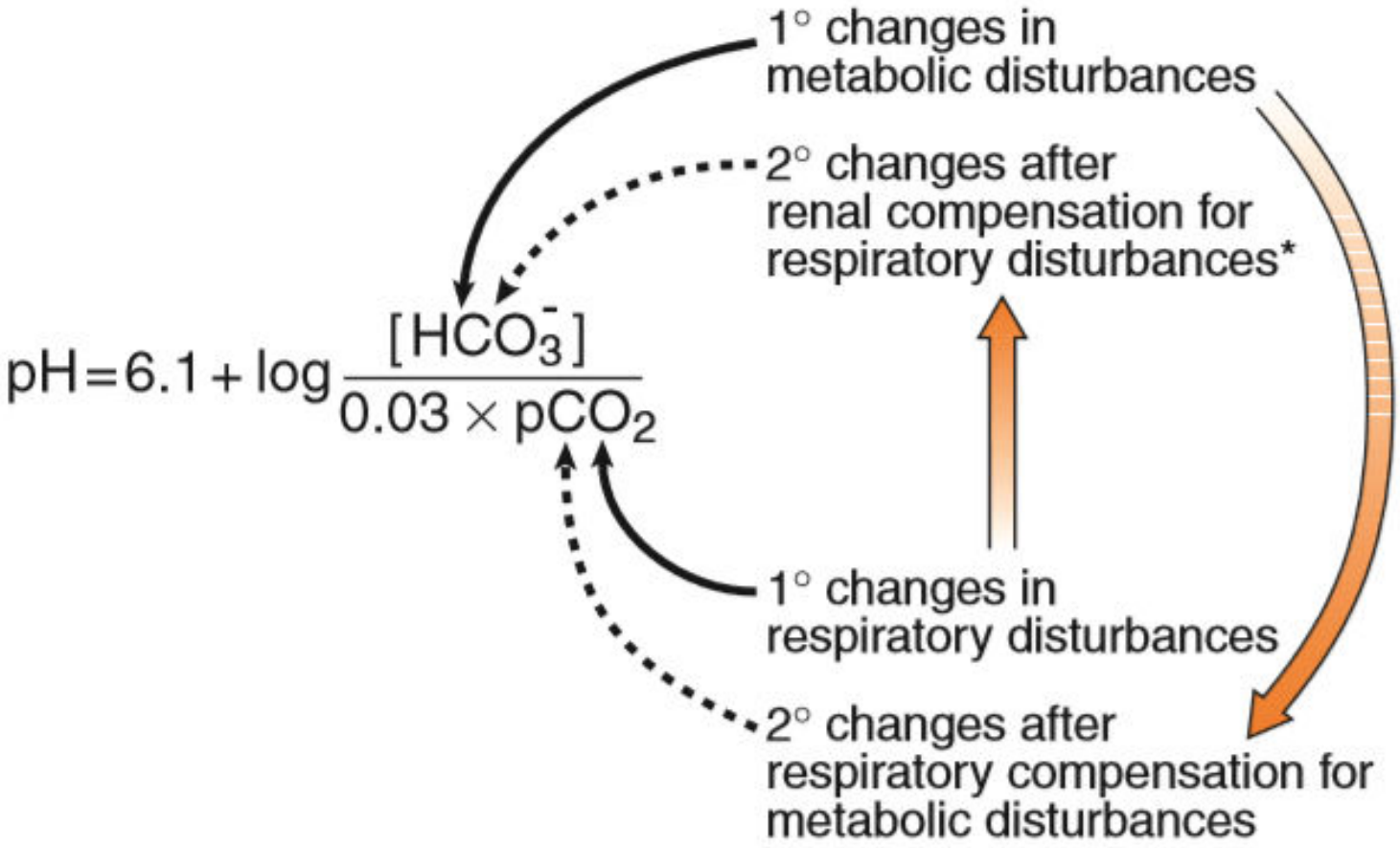
Acid-Base Imbalances

- pH< 7.35 acidosis
- pH > 7.45 alkalosis
- The body response to acid-base imbalance is called **compensation**
- May be **complete** if brought back within normal limits
- **Partial compensation** if range is still outside normals
- If underlying problem is metabolic, hyperventilation or hypoventilation can help : **respiratory compensation**.
- If problem is respiratory, renal mechanisms can bring about **metabolic compensation**

Definitions

- Acidosis: process that lowers the extracellular fluid pH (reduction in HCO_3 or elevation in pCO_2)
  - Metabolic acidosis: **low pH and low HCO_3**
  - Respiratory acidosis: **low pH and high pCO_2**

- Alkalosis: process that raises extracellular pH (elevation in HCO_3 or fall in pCO_2)
  - Metabolic alkalosis: **high pH and high HCO_3**
  - Respiratory alkalosis: **high pH and low pCO_2**


1° changes in metabolic disturbances
2° changes after renal compensation for respiratory disturbances*
$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times pCO_2}$
1° changes in respiratory disturbances
2° changes after respiratory compensation for metabolic disturbances

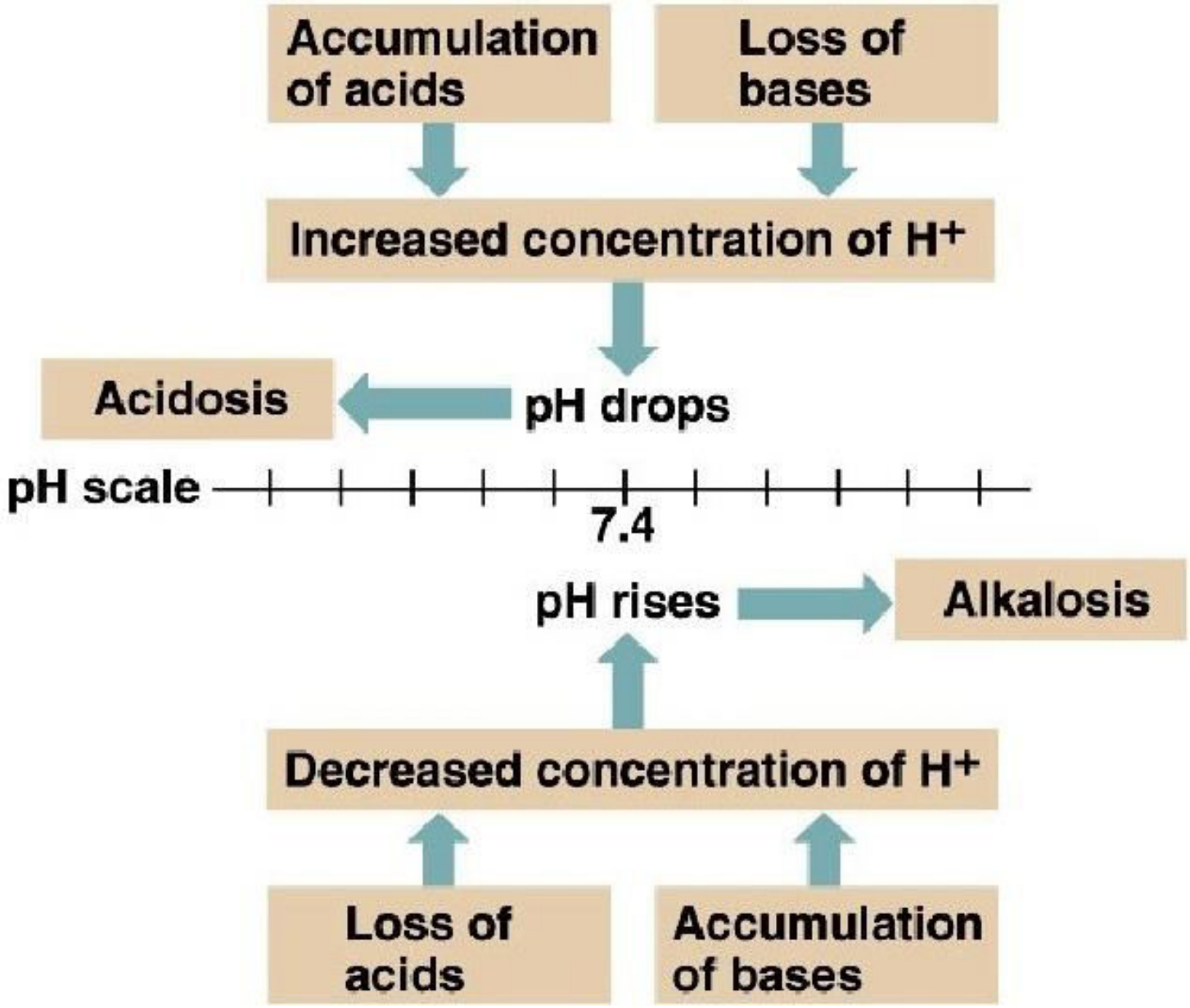
Keep It Simple

- $PaCO_2$ = Acid
  - ↑ $PaCO_2$ = ↓ pH (Acidemia)
  - ↓ $PaCO_2$ = ↑ pH (Alkalemia)

- HCO_3 = Base
  - ↑ HCO_3 = ↑ pH (Alkalemia)
  - ↓ HCO_3 = ↓ pH (Acidemia)

- Acidosis: pH < 7.35
  - Respiratory PaCO > 40 mmHg
  - Metabolic HCO_3 < 24 mEq/L

- Alkalosis: pH > 7.45
  - Respiratory $PaCO_2$ < 40 mmHg
  - Metabolic HCO3 >24 mEq/L


Accumulation of acids
Loss of bases
Increased concentration of H+
Acidosis
pH drops
pH scale
7.4
pH rises
Alkalosis
Decreased concentration of H+
Loss of acids
Accumulation of bases

Respiratory Acidosis

- **Carbonic acid excess** caused by blood levels of CO_2 above 45 mm Hg.
- **Hypercapnia** – high levels of CO_2 in blood

Causes:

- Chronic conditions:
  - Depression of respiratory center in brain that controls breathing rate – drugs or head trauma
  - Paralysis of respiratory or chest muscles
  - COPD, pneumonia & obesity

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Respiratory Acidosis

- Acute conditons:
  - Adult Respiratory Distress Syndrome
  - Pulmonary edema
  - Pneumothorax
  - Pulmonary emboli
  - Aspiration pneumonia
  - Increased CO2 production (Malignant hyperthermia & thyroid storm)

Signs and Symptoms of Respiratory Acidosis

- Breathlessness
- Restlessness
- Lethargy and disorientation
- Tremors, convulsions, coma
- Respiratory rate rapid, then gradually depressed
- Skin warm and flushed due to vasodilation caused by excess CO_2

Compensation for Respiratory Acidosis

- This is accomplished via two mechanisms;

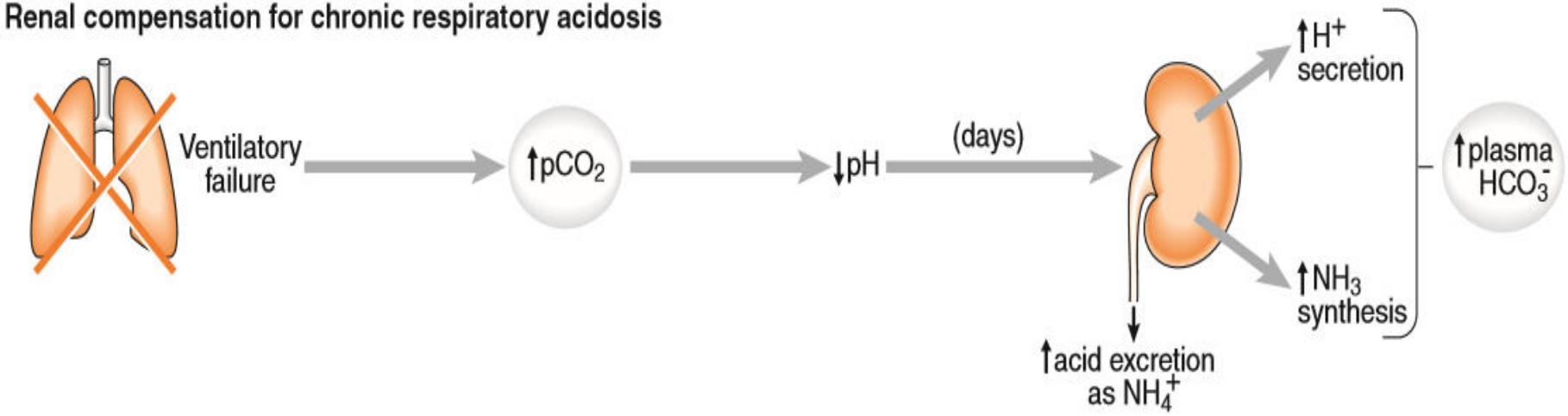
a) rapid cell buffering and

- In this setting, carbonic acid (H_2CO_3) can only be buffered by the limited **intracellular buffers (primarily hemoglobin and proteins).**

$$H_2CO_3 + Hb^- \rightarrow HHb + \mathbf{HCO_3^-}$$

b) an increase in net acid excretion.

- **Kidneys** eliminate hydrogen ion and retain bicarbonate ion (Chronic state)


Renal compensation for chronic respiratory acidosis
Ventilatory failure
↑pCO2
↓pH
(days)
↑H+ secretion
↑NH3 synthesis
↑acid excretion as NH4+
↑plasma HCO3-

Respiratory Alkalosis

- Carbonic acid deficit
- pCO_2 less than 35 mm Hg (hypocapnea)
- Most common acid-base imbalance
- Primary cause is hyperventilation

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Respiratory Alkalosis

- Conditions that stimulate respiratory center:
  - Oxygen deficiency at high altitudes
  - Pulmonary disease and Congestive heart failure – cau by hypoxia
  - Acute anxiety & pain
  - Fever, anemia

Signs and Symptoms of Respiratory Alkalosis

- Alkalosis causes over excitability of the central and peripheral nervous systems.
- **Numbness**
- Light headedness
- It can cause :
  - Nervousness
  - **muscle spasms or tetany**
  - **Convulsions**
  - Loss of consciousness
  - Death

Compensation of Respiratory Alkalosis

- There are two mechanisms responsible for this compensation to respiratory alkalosis;

1) Rapid cell buffering and

2) Decrease in net renal acid excretion.

- **hydrogen ions move from the cells into the extracellular fluid, where they combine with [HCO_3- to form carbonic acid in the following reaction:**

$$H^+ + HCO_3^- \rightarrow H_2CO_3 \text{ (CA)}$$

Metabolic Acidosis

- **Bicarbonate deficit** - blood concentrations of bicarb drop below 22mEq/L
- Occurs when pH falls below 7.35
- **Causes:**
  - Loss of bicarbonate through diarrhea or renal dysfunction
  - Accumulation of acids (lactic acid or ketones)
  - Failure of kidneys to excrete H+

Two types of Metabolic Acidosis

- **High Anion Gap** = net gain of acid
- **Normal anion gap** = loss of bicarbonate

Anion Gap Calculation

- $[Na^+ + K^+] - [Cl + HCO3]$ (Normal = 12 ± 2)

E.g :- Na 140, k 4 , CL 114, HCO3 18

(140 + 4) – (114 + 18)

144 – 132 = 12 **normal**

E.g:- Na 140 , Cl 104, K 4.0, HCO3 10

(144) – (114) = 30 **= High anion gap**

Normal Anion Gap
(USED CARP)

- Ureterostomy
- Small bowel fistula
- Extra Chloride
- Diarrhea
- Carbonic anhydrase inhibitors
- Addison's disease
- Renal tubular acidosis
- Pancreatic fistulas

  Treatment: Replace Bicarbonate

High Anion Gap Differential
(MUDPILES)

- Methanol
- Uremia
- DKA
- Paraldehyde
- Inborn Errors
- Lactic Acidosis
- Ethylene Glycol
- Salicylates

Symptoms of Metabolic Acidosis

- Headache, lethargy
- Nausea, vomiting, diarrhea
- Coma
- Death

Compensation for Metabolic Acidosis

- Increased ventilation
- Renal excretion of hydrogen ions if possible
- K^+ exchanges with excess H^+ in ECF

(H^+ into cells, K^+ out of cells)

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Metabolic Alkalosis

- **Characterized by**
  - **Primary ↑ in HCO3 concentration greater than 26 mEq/L**
  - **Compensatory ↑ in PaCO2**

Metabolic Alkalosis

Causes

- **Volume Contraction:**
  - **Nasogastric suctioning, Gastric fistula**
  - **Vomiting , pyloric stenosis**

- **Alkali ingestion**

Symptoms of Metabolic Alkalosis

- Respiration slow and shallow
- Hyperactive reflexes ; tetany
- Often related to depletion of electrolytes
- Dysrhythmias

Compensation

- The development of alkalemia is sensed by central and peripheral chemoreceptors, resulting in a reduction in the rate of ventilation and a reduction in tidal volume and thus an elevation in the pCO_2.

Compensation

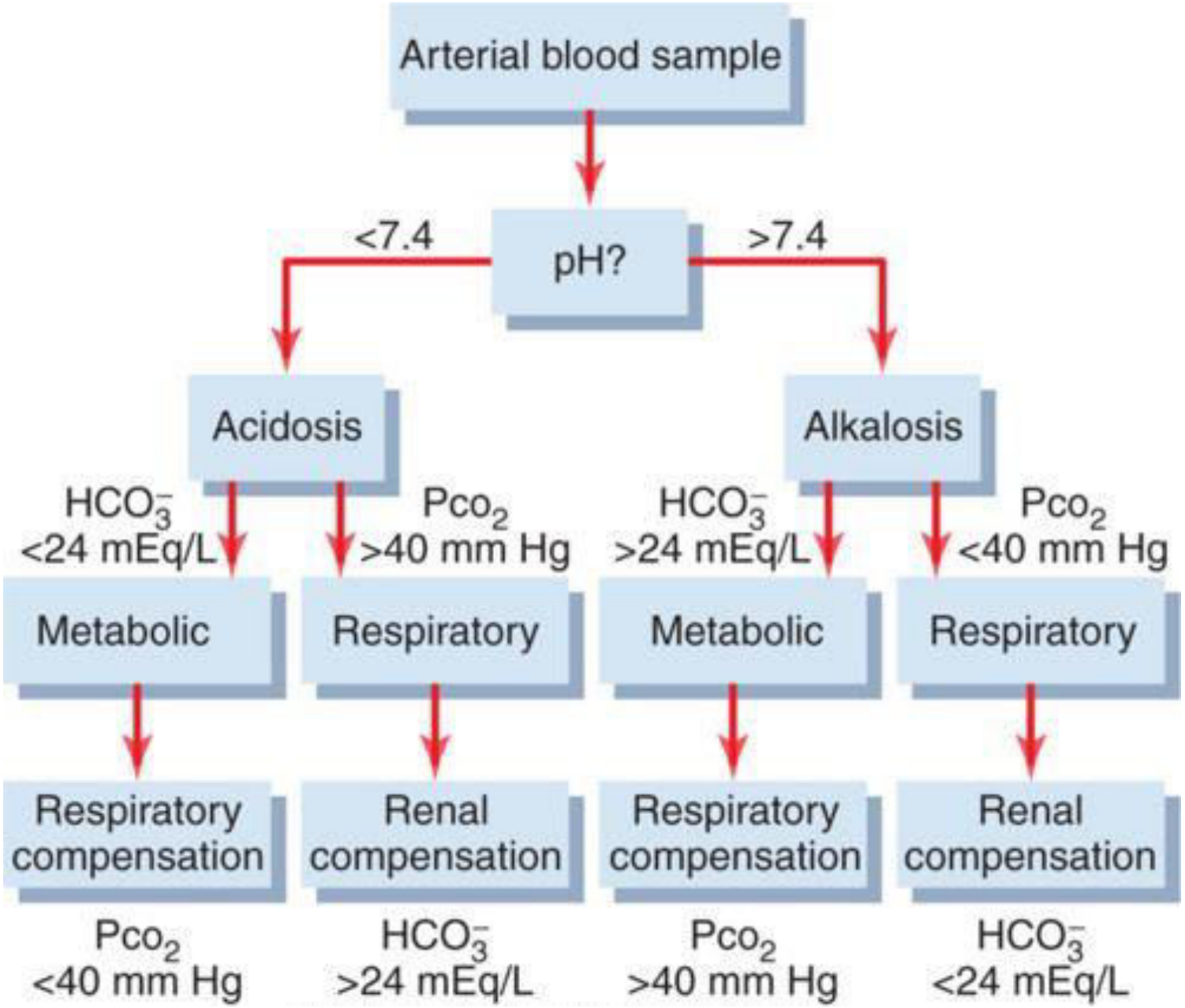
Primary Disorder	Compensatory Mechanism
Metabolic acidosis	Increased ventilation
Metabolic alkalosis	Decreased ventilation
Respiratory acidosis	Increased renal reabsorption of HCO_3^- in the proximal tubule Increased renal excretion of H in the distal tubule
Respiratory alkalosis	Decreased renal reabsorption of HCO_3^- in the proximal tubule Decreased renal excretion of H^+ in the distal tubule

Acid Base Disorders

Disorder	pH	$[H^+]$	Primary disturbance	Secondary response
Metabolic acidosis	↓	↑	↓ $[HCO_3^-]$	↓ pCO_2
Metabolic alkalosis	↑	↓	↑ $[HCO_3^-]$	↑ pCO_2
Respiratory acidosis	↓	↑	↑ pCO_2	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓ pCO_2	↓ $[HCO_3^-]$

A 31 year old man presents with lethargy, weakness, labored respiration, and confusion. He has had diabetes for 15 years, When seen in the emergency department his urine dipped positive for both glucose and ketones and his breath had a strange sweet, fruity smell. The following arterial blood gas data was obtained:
pH 7.27
PCO_2 23 mm Hg
Na^+ 132 mEq/L
Cl^- 83 mEq/L
K^+ 4.9 mEq/L
HCO_3 10 mEq/L
Glucose 345 mg/dL

- A 26-year-old woman is undergoing treatment for frequent panic attacks. The attacks are accompanied by hyperventilation,a racing heartbeat (tachycardia),dizziness, feelings of “unreality” and tingling in the hands. In one particularly severe attack, when taken to the emergency department, an arterial blood-gas sample was taken, which revealed the following:
- pH 7.52
- PCO2 26 mm Hg
- HCO3 22 mEq/L
- What is the metabolic disturbance?


Arterial blood sample
pH?
<7.4
>7.4
Acidosis
Alkalosis
HCO_3^- <24 mEq/L
Pco_2 >40 mm Hg
HCO_3^- >24 mEq/L
Pco_2 <40 mm Hg
Metabolic
Respiratory
Metabolic
Respiratory
Respiratory compensation
Renal compensation
Respiratory compensation
Renal compensation
Pco_2 <40 mm Hg
HCO_3^- >24 mEq/L
Pco_2 >40 mm Hg
HCO_3^- <24 mEq/L