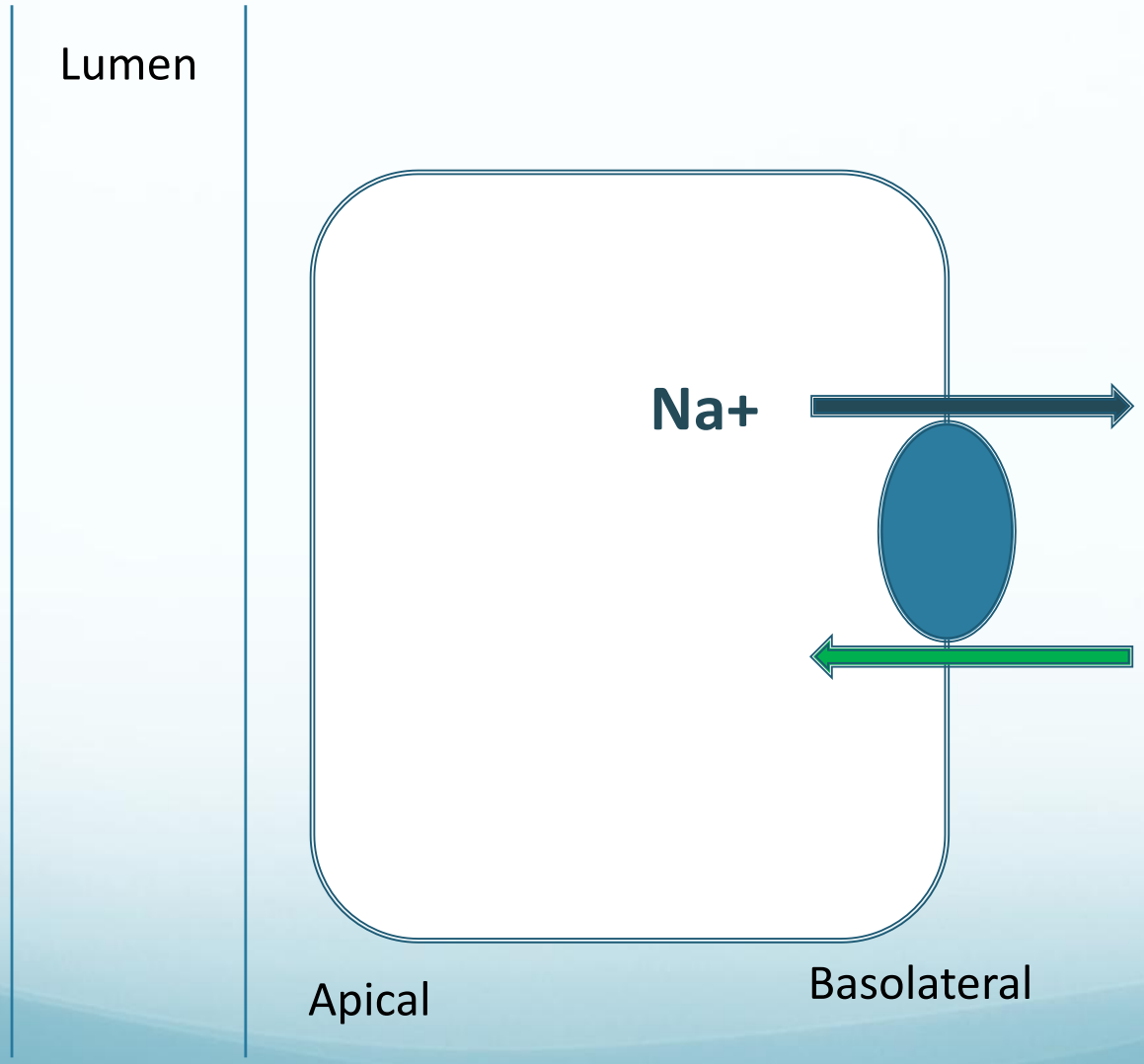
# Cellular Basis of Transport

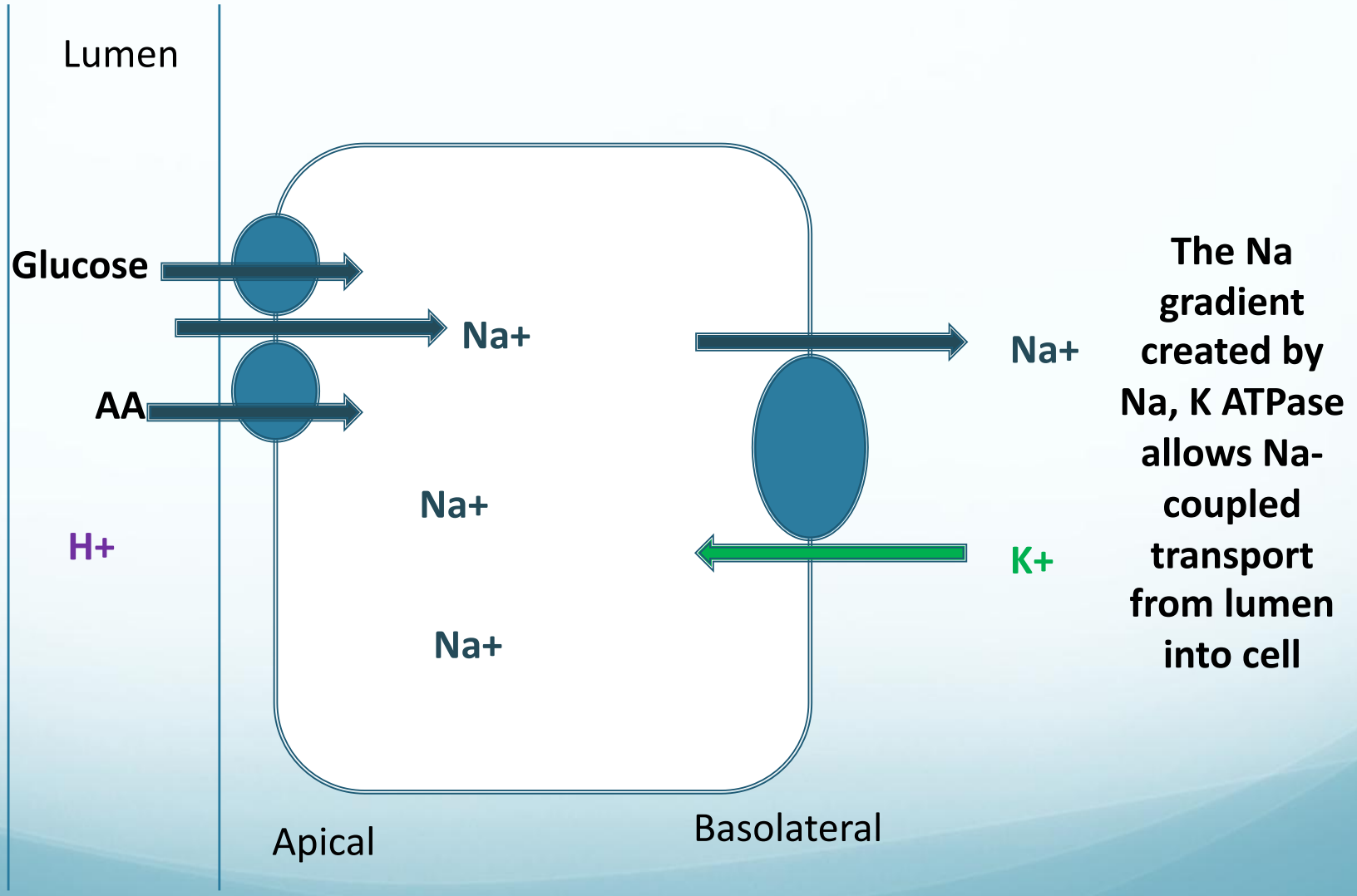
- Summarize key examples of transport proteins
- Examples:
  - Sodium
  - Chloride
  - bicarbonate
- Describe mechanisms of diarrhea

# Na, K ATPase



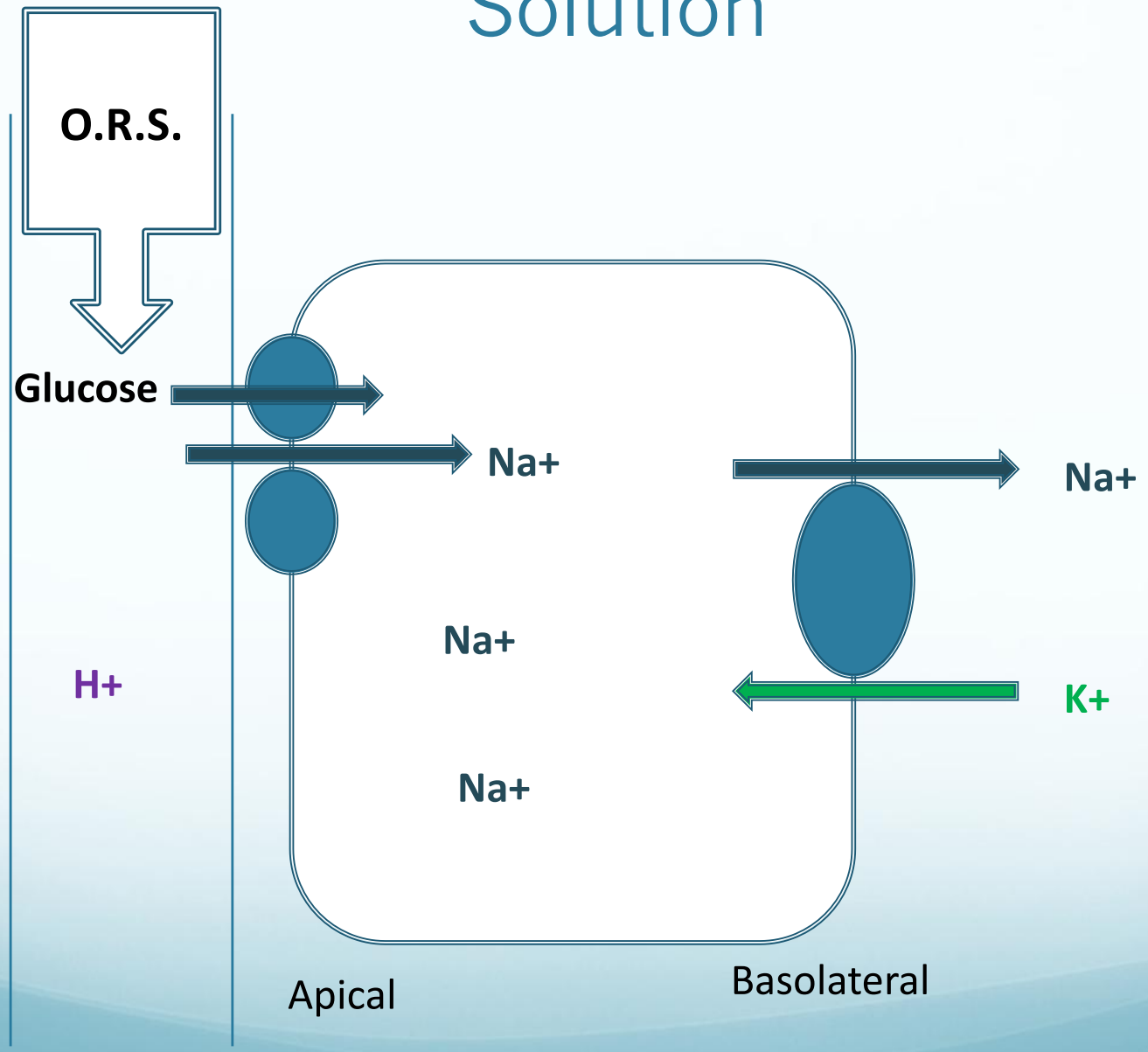

**Na, K ATPase creates a Na electrochemical gradient between enterocyte and lumen**

# Na Coupled Transport

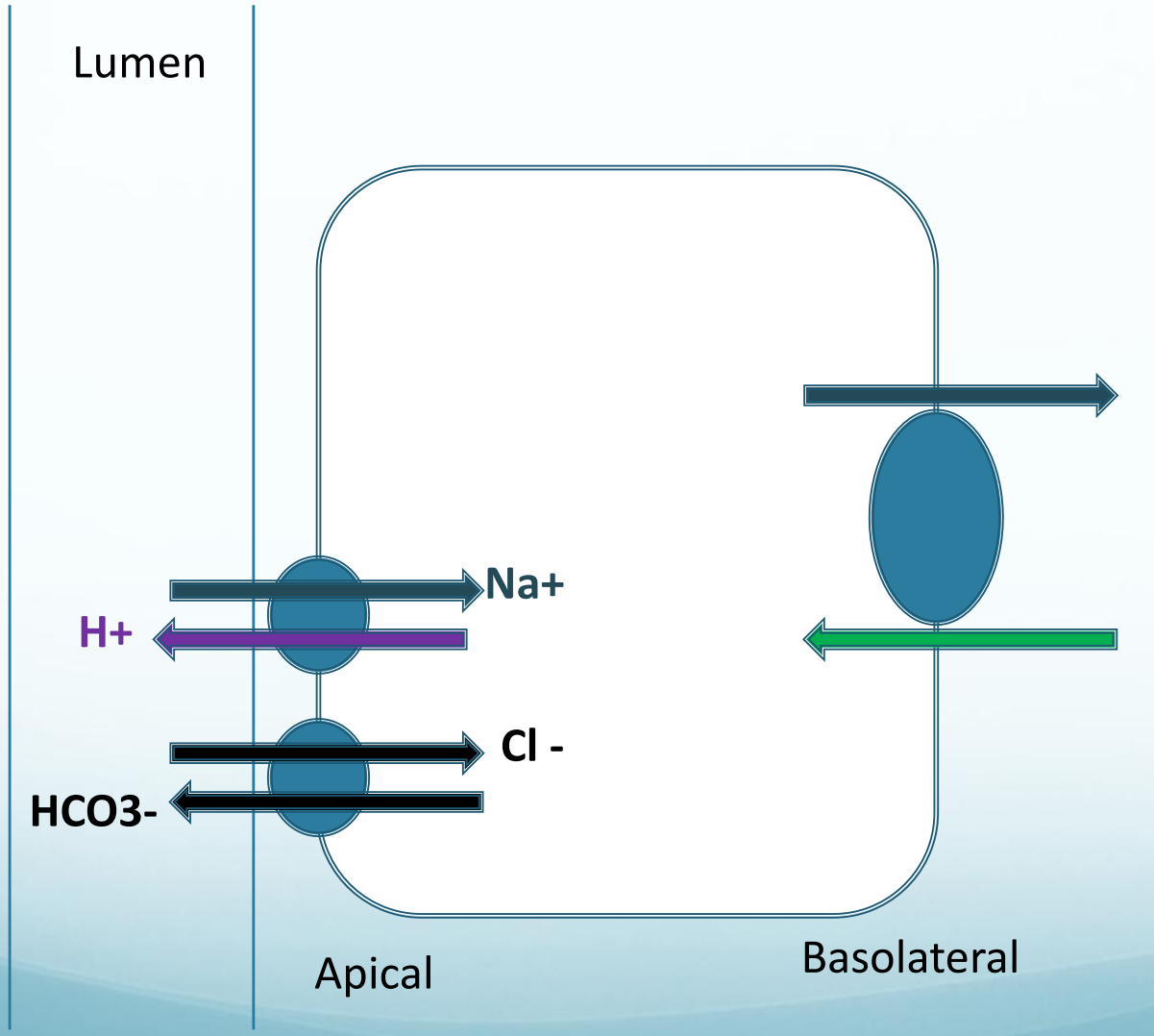



**The Na gradient created by Na, K ATPase allows Na-coupled transport from lumen into cell**

# Clinical Application: Oral Rehydration Solution

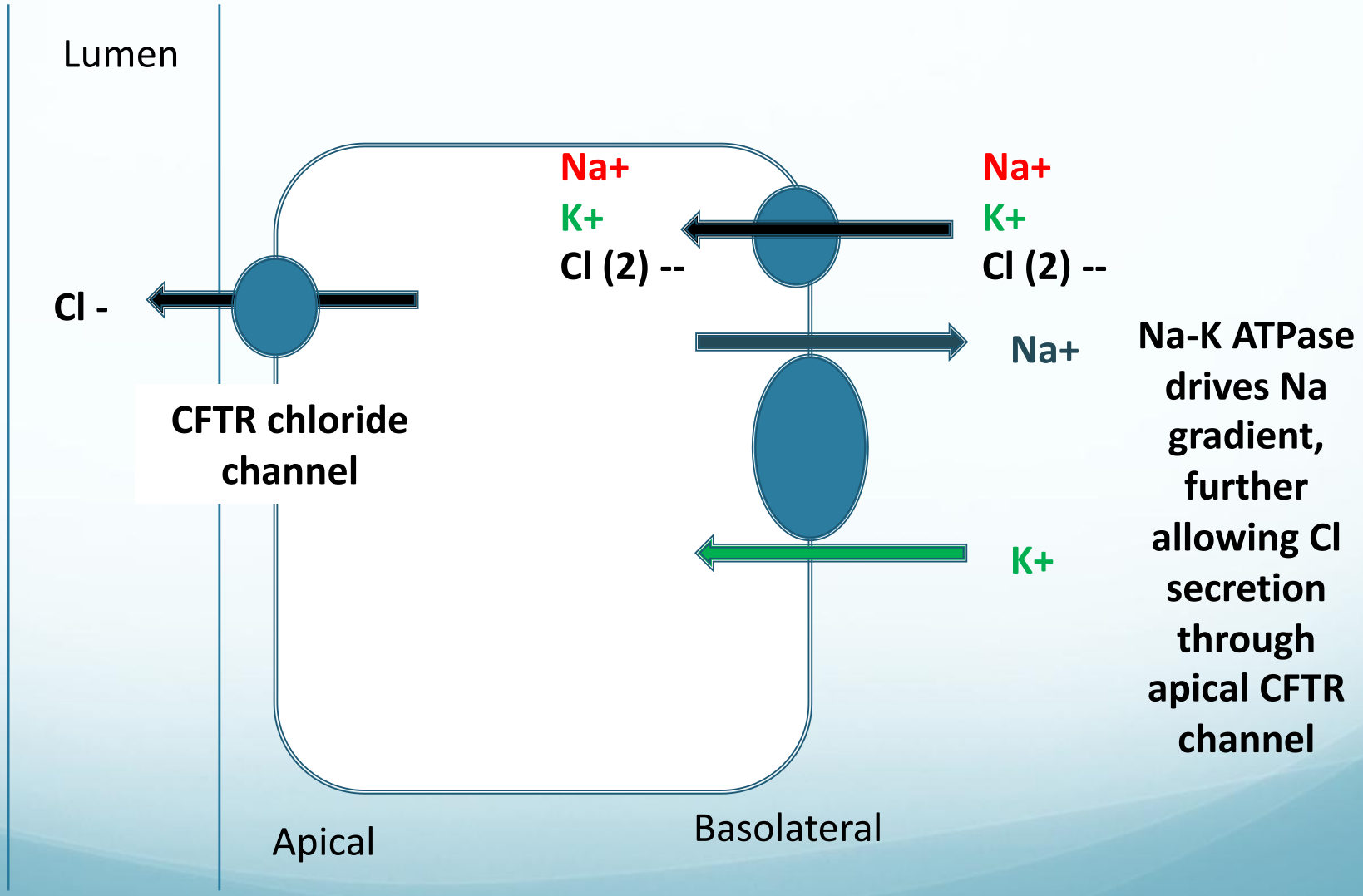


# NaCl Co-transport is mediated by TWO transport proteins

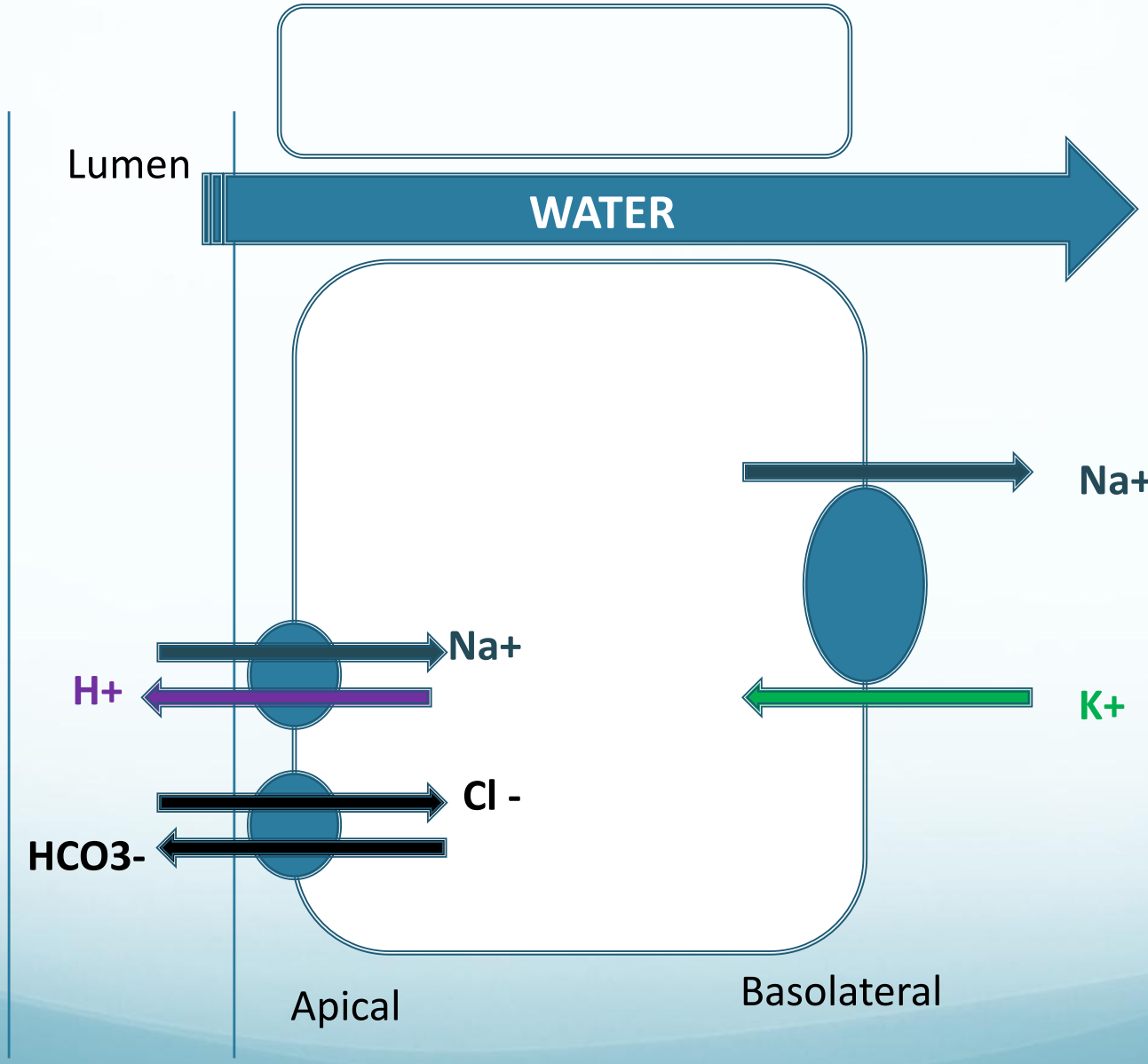



**Na/H (cation) exchanger works in conjunction with HCO3/Cl (anion) exchanger, allowing NaCl absorption**

# Concept 4: Chloride secretion occurs in conjunction with basolateral Na, K, Cl transport



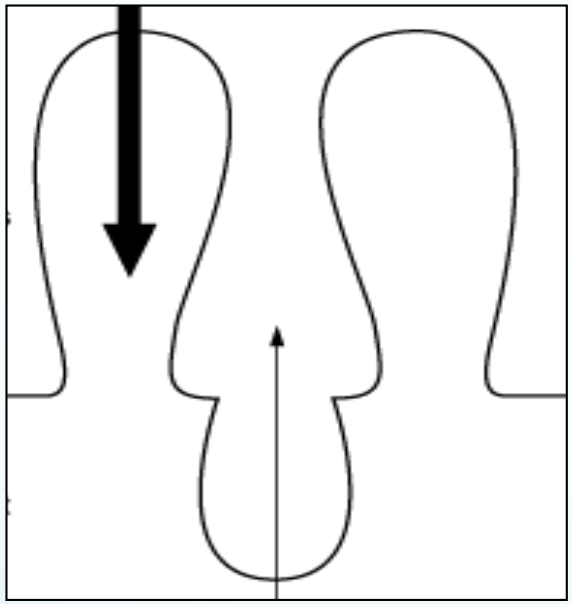
# Water follows NaCl




**Water will travel through intercellular tight junctions in the setting of NaCl absorption**

# Absorption and Secretion in Health versus Diarrheal States

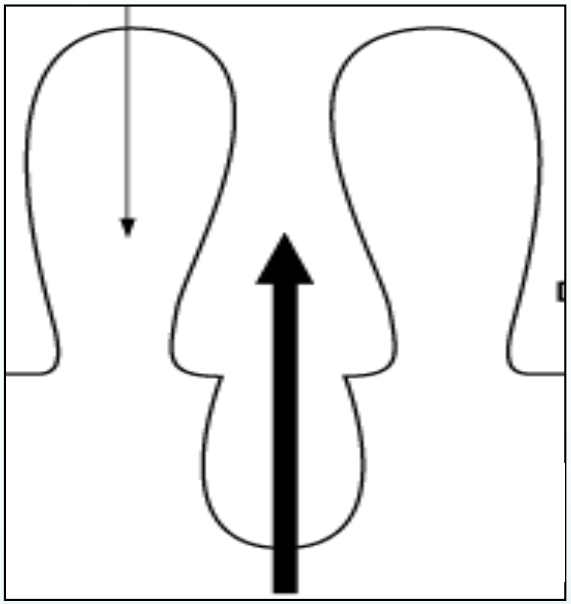
**NaCl, Nutrient absorption**



Chloride secretion

Healthy

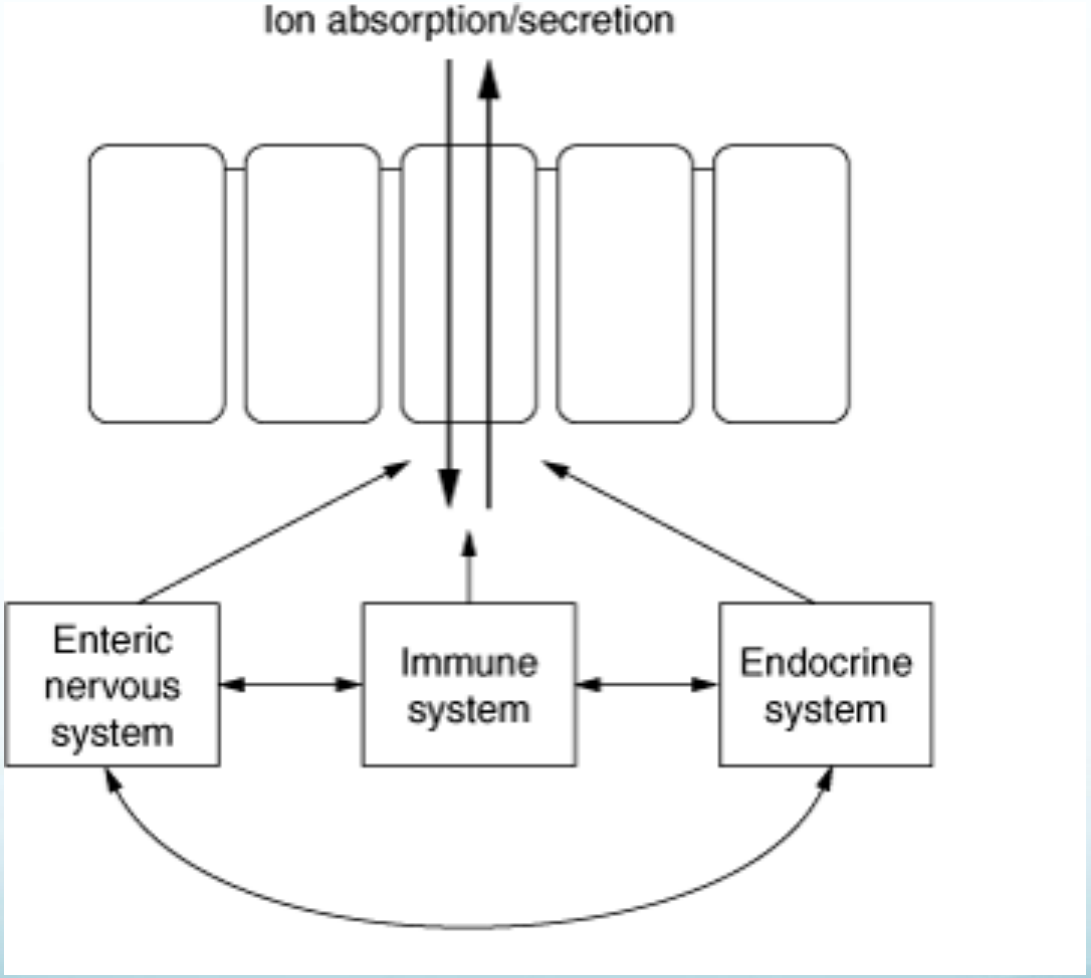
NaCl absorption



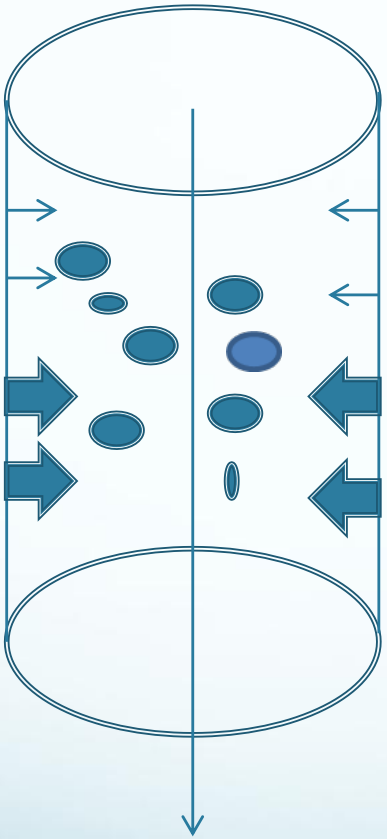
**Chloride Secretion**

Diarrhea

# Multiple Systems Interact in Regulation of Ion Transport and Secretion

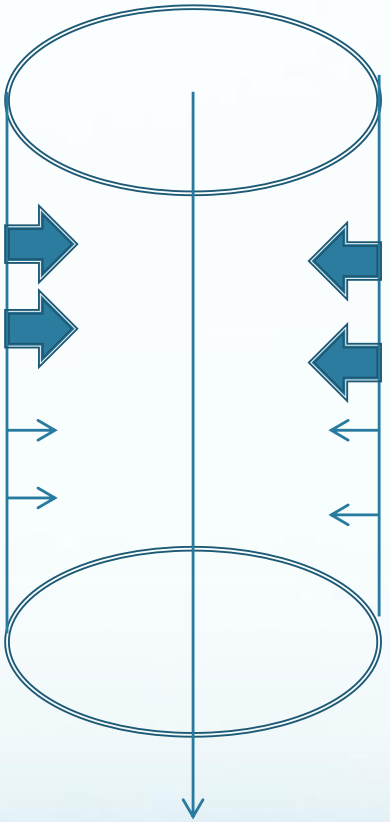


# Mechanisms of Diarrhea: Osmotic versus Secretory



Small Intestine

Colon



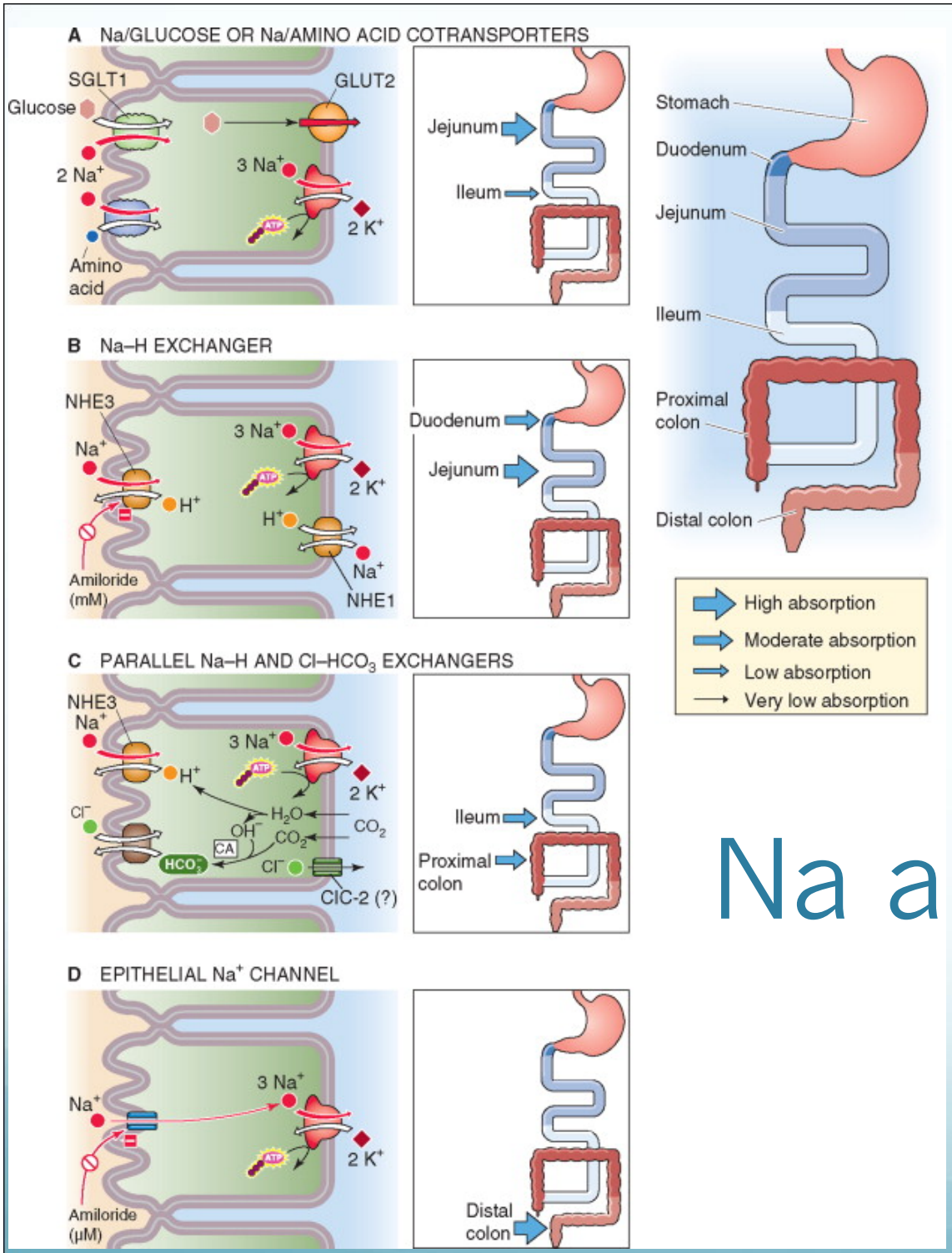
Osmotic Diarrhea:
Solute-driven water losses more prominent in the colon

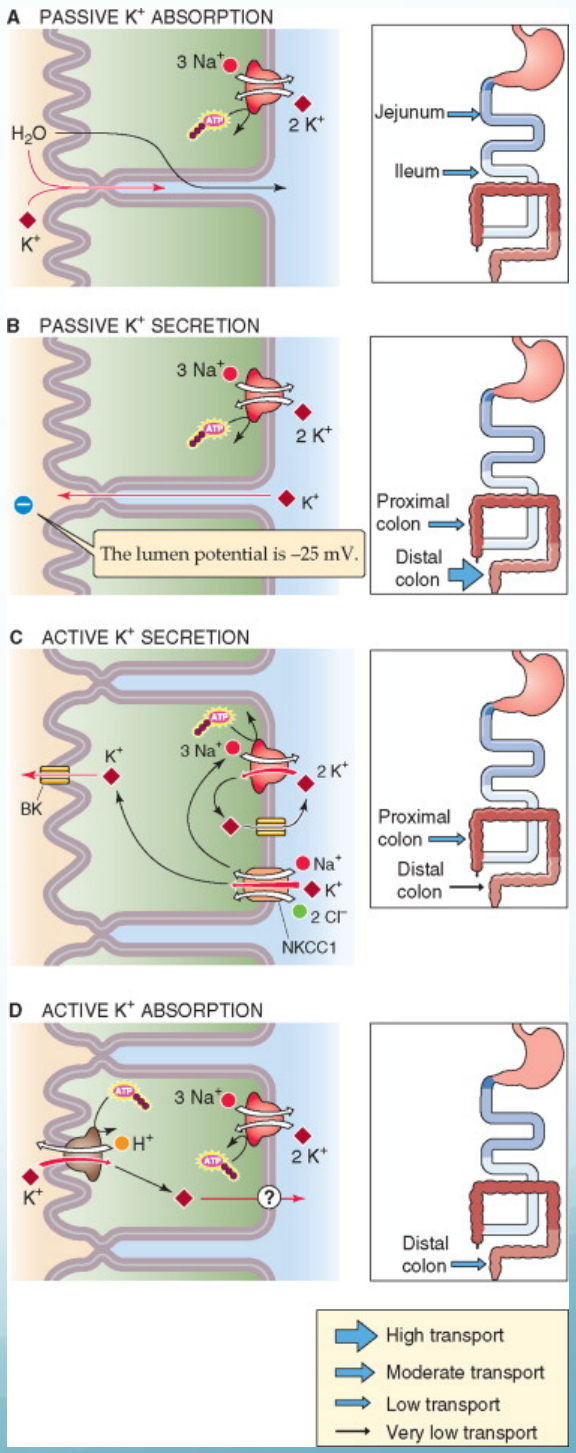
Secretory Diarrhea:
Crypt secretion leads to more prominent small intestinal losses

# Mechanisms of Bacterial Pathogens

| Signal/pathway | Examples | Mechanism |
|---|---|---|
| cAMP | Cholera toxin<br>Heat labile E Coli (ETEC) | Blocks NaCl absorption<br>Stimulates anion secretion |
| cGMP | Heat stable E Coli (EAEC)<br>Klebsiella | Blocks NaCl absorption<br>Stimulate anion secretion |
| Ca++ / protein kinase C | C Difficile enterotoxin | |
| Pore forming toxin | Staph Aureus α-toxin<br>C. perfringes | Pore formation along brush border membrane |
| Toxin blocking protein synthesis | EHEC Shiga toxin<br>Shigella Shiga toxin | A1 subunit of toxin binds ribosome and interrupts protein synthesis |
| Toxin inducing protein synthesis | Staph toxin A<br>EAggEC toxin | Upregulate proinflammatory cytokines |
| Toxin affecting cytoskeleton | Clostridium species | |

# Na and K

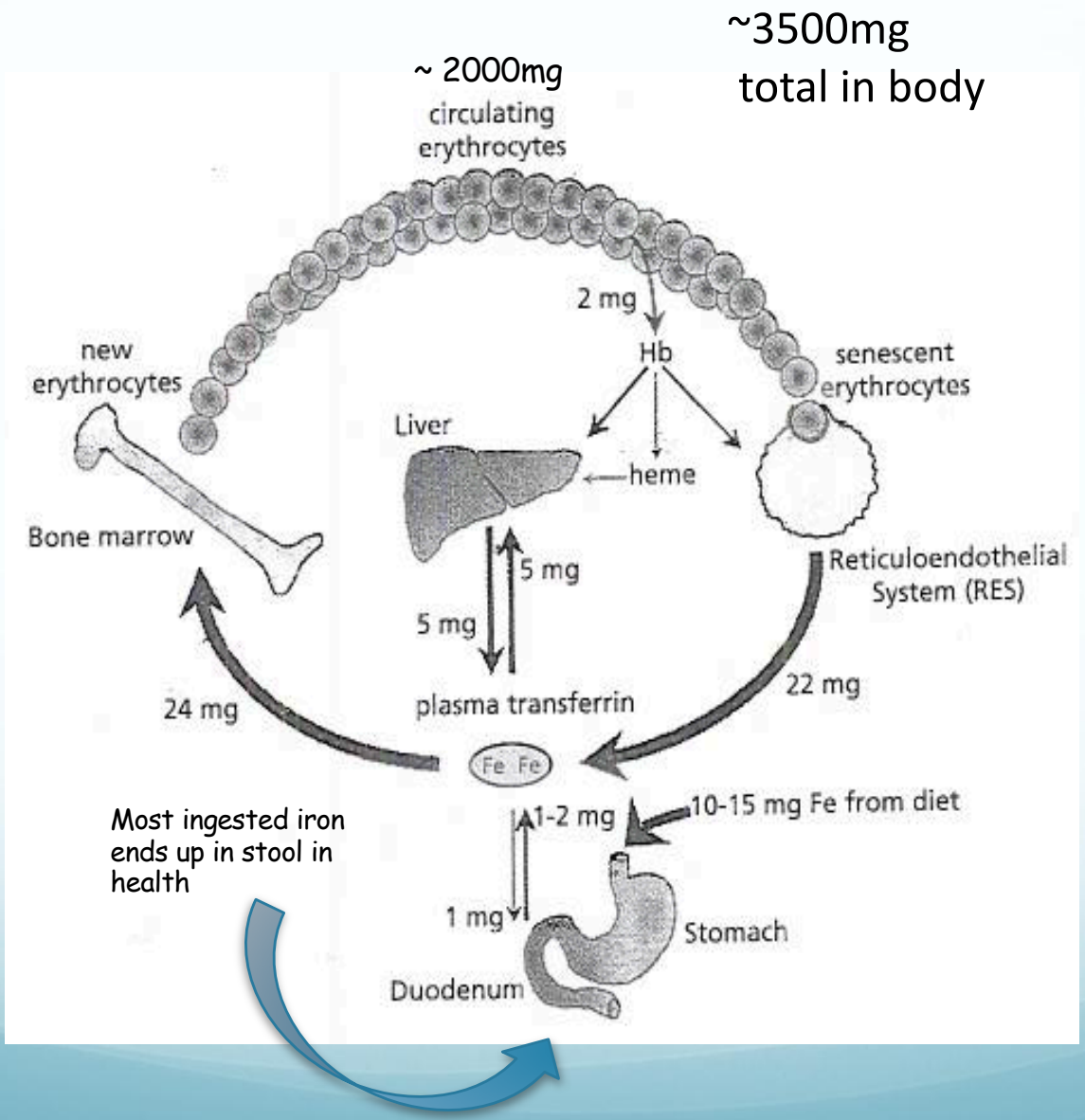

A Na/GLUCOSE OR Na/AMINO ACID COTRANSPORTERS
SGLT1
GLUT2
Glucose
2 Na+
3 Na+
2 K+
Amino acid
Jejunum
Ileum
B Na–H EXCHANGER
NHE3
Na+
3 Na+
2 K+
H+
H+
Na+
Amiloride (mM)
NHE1
Duodenum
Jejunum
C PARALLEL Na–H AND Cl–HCO3 EXCHANGERS
NHE3
Na+
3 Na+
2 K+
H+
Cl−
H2O
CO2
OH−
CO2
CA
HCO3−
Cl−
ClC-2 (?)
Ileum
Proximal colon
D EPITHELIAL Na+ CHANNEL
Na+
3 Na+
2 K+
Amiloride (μM)
Distal colon
Stomach
Duodenum
Jejunum
Ileum
Proximal colon
Distal colon
High absorption
Moderate absorption
Low absorption
Very low absorption


A PASSIVE K+ ABSORPTION
3 Na+
2 K+
H2O
K+
Jejunum
Ileum
B PASSIVE K+ SECRETION
3 Na+
2 K+
K+
The lumen potential is –25 mV.
Proximal colon
Distal colon
C ACTIVE K+ SECRETION
K+
3 Na+
2 K+
BK
Na+
K+
2 Cl−
NKCC1
Proximal colon
Distal colon
D ACTIVE K+ ABSORPTION
3 Na+
2 K+
H+
K+
?
Distal colon
High transport
Moderate transport
Low transport
Very low transport

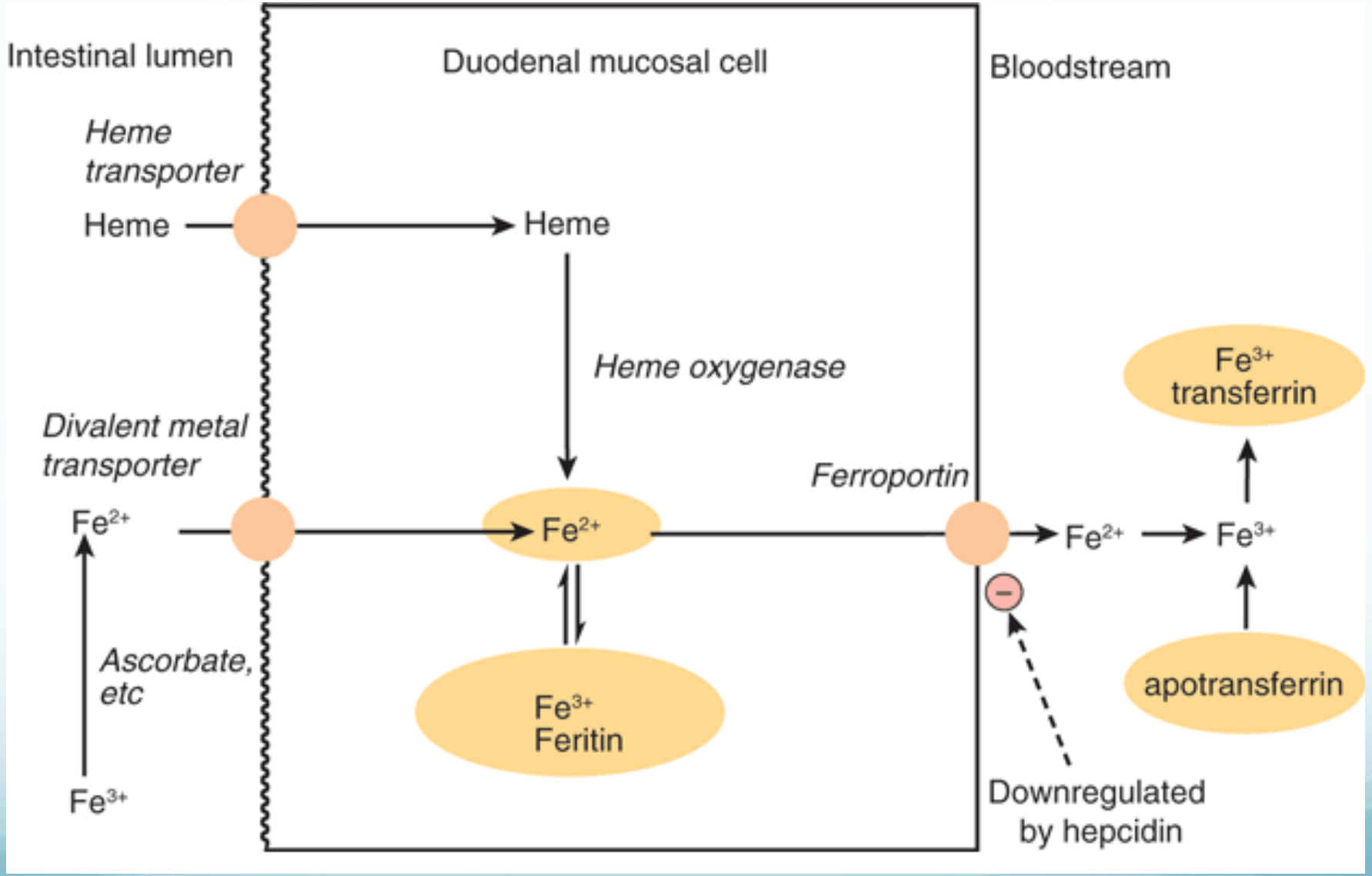
# Minerals and Vitamins

- Iron
- Calcium
- Magnesium
- Water Soluble Vitamins
- Fat Soluble Vitamins

# Iron Metabolism and Balance

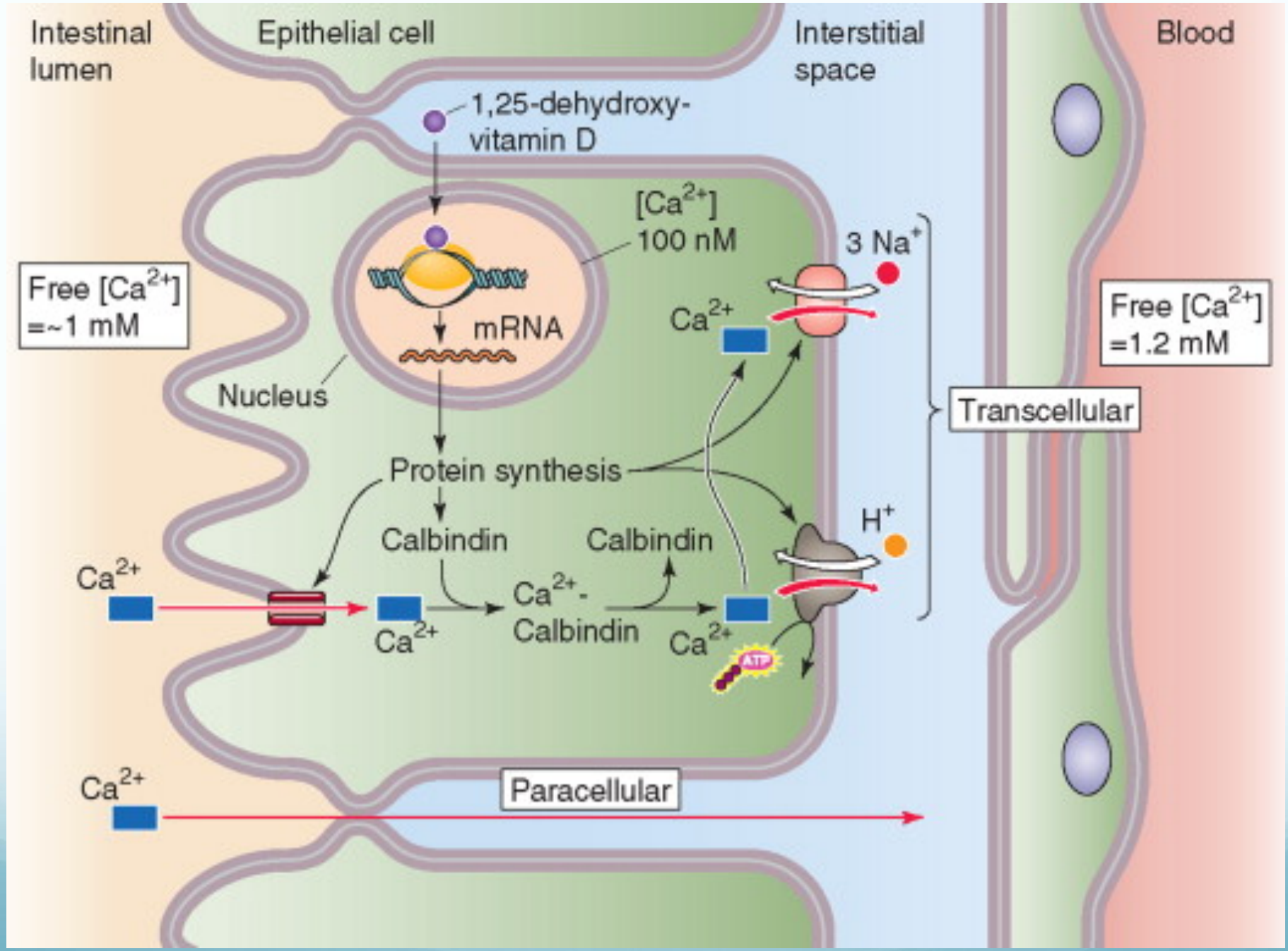


# Iron Absorption



# Calcium and Magnesium Absorption

- Calcium
  - Absorbed primarily in duodenum
  - 1,25 OH Vit D regulates:
    - Enterocyte apical Ca Channel
    - Intracellular protein calbindin (shepards to export pump)
    - Basolateral Ca-ATPase
  - Vit D independent transport follows concentration gradient
- Magnesium
  - Absorbed throughout GI tract
  - Regulation of Mg absorption is dependent on dietary intake
  - Mg Channel upregulated in low Mg states to promote absorption


Intestinal lumen
Epithelial cell
Interstitial space
Blood
1,25-dehydroxy-vitamin D
[Ca2+] 100 nM
Free [Ca2+] =~1 mM
mRNA
Nucleus
3 Na+
Ca2+
Free [Ca2+] =1.2 mM
Transcellular
Protein synthesis
Calbindin
Calbindin
H+
Ca2+
Ca2+
Ca2+-Calbindin
Ca2+
ATP
Ca2+
Paracellular

# Water Soluble Vitamins

- Vitamin C
- B vitamins
  - Thiamine
  - Riboflavin
  - Niacin
  - B6
  - Folate
  - B12
  - Biotin
  - Pantothenic acid

- Water soluble
- Taken up easily by cells (B12 requires IF)
- In general, water soluble vitamins are not stored in tissue
  - Exclusions: B12 (liver storage)

# Fat Soluble Vitamins

- A
- D
- E
- K

- Digested, absorbed, and transported with dietary fat
- Stored in liver, fat cells

| Micronutrient | Pathophysiology | Clinical deficiency syndrome | Clinical overload syndrome | Laboratory evaluation |
|---|---|---|---|---|
| Minerals and trace elements | | | | |
| Calcium | Fat malabsorption | Paresthesias, tetany, bone demineralization | *GI, GU, bone complaints | Serum Ca, PTH, DEXA scan |
| Magnesium | Fat malabsorption and high GI fluid losses | Weakness, cardiac, CNS | *Weakness, cardiac | Serum Mg |
| Zinc | GI fluid losses | Poor growth, skin, hair, diarrhea | *Vomiting, headache, diarrhea, Cu deficiency | Serum Zn, low alkaline phosphatase |
| Copper | Overload more common in cholestasis | *Hemolytic anemia, neutropenia | Hepatic overload, neuropsychiatric | Serum Cu |
| Manganese | Overload more common in cholestasis | *Poor growth, ataxia, skeletal | Neurotoxicity | Serum Mn |
| Iron | Absorbed proximally; not routinely in TPN | Microcytic anemia, irritability | Hepatotoxicity, GI bleeding, vomiting | Ferritin, TIBC, Iron Binding Cap, Hgb, HCT, peripheral smear |
| Selenium | Absorbed throughout small bowel | Myopathy, cardiomyopathy | *Thyroid enlargement | Serum selenium |
| Fat-soluble vitamins | | | | |
| A | Fat malabsorption, cholestasis | Xerophthalmia, blindness | Increased ICP, hepatitis, vomiting | Vitamin A: retinol binding protein ratio |
| D | Fat malabsorption, cholestasis | Hypocalcemia, hypophosphatemia, rickets | Emesis, renal impairment | 25-OH vitamin D |
| E | Fat malabsorption, cholestasis | Myopathy, neuropathy, ataxia, hemolytic anemia | coagulopathy | Vitamin E: total serum lipid ratio |
| K | Fat malabsorption, cholestasis | Bleeding | Hemolytic anemia | Prothrombin time, PIVKA assay |
| Water-soluble vitamins | | | | |
| B12 | Gastric or ileal resection | Megaloblastic anemia, CNS including ataxia | None known | Serum B12, methylmalonic acid, homocysteine |
| Folate | Absorbed proximally | Anemia, thrombocytopenia, stomatitis, glossosis | None known | Serum Folate |

# Intestinal Brush Border Enzyme Deficiencies

- Deficiency of brush border disaccharidases
- Disaccharides not hydrolyzed at mucosal cell membrane

# Intestinal Brush Border Enzyme Deficiencies

- May occur as
  - Rare congenital defects
    - Lack of sucrase, isomaltase, lactase in newborns
  - Secondary to diseases that damage intestinal epithelium
    - Crohn's disease, celiac disease
  - Genetic form
    - Lactase deficiency

# Lactase “Deficiency”

- 70% of adults worldwide are lactase deficient, especially Africans, South Americans, and Asians
- Maintenance of lactase into adulthood is probably the result of a genetic mutation
- Diagnosed based on history of  GI intolerance to dairy products

# Lactose Intolerance Diagnostics

Lactose breath hydrogen test

- Baseline breath hydrogen concentration is measured.
- Patient consumes 25 to 50 grams lactose.
- Breath hydrogen concentration is re-measured in 3 to 8 hours. An increase >20 ppm suggests lactose malabsorption (90% sensitivity).

# Lactose Deficiency Diagnostics

Lactose tolerance test

- After 8-hour fast, baseline serum glucose is measured.
- Patient consumes 50-100 grams of lactose
- Serum blood glucose levels are measured at 30, 60, and 90 minutes after lactose ingestion
- No increase in blood glucose levels suggests lactose malabsorption (Pagana, 2004).