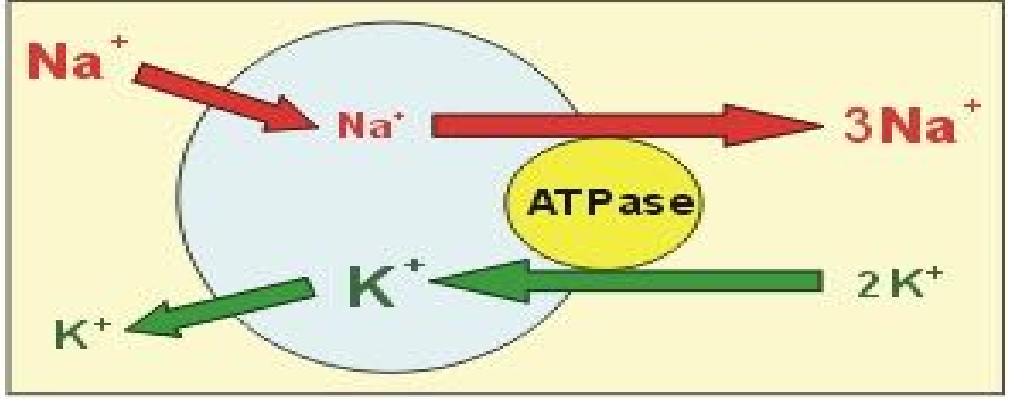
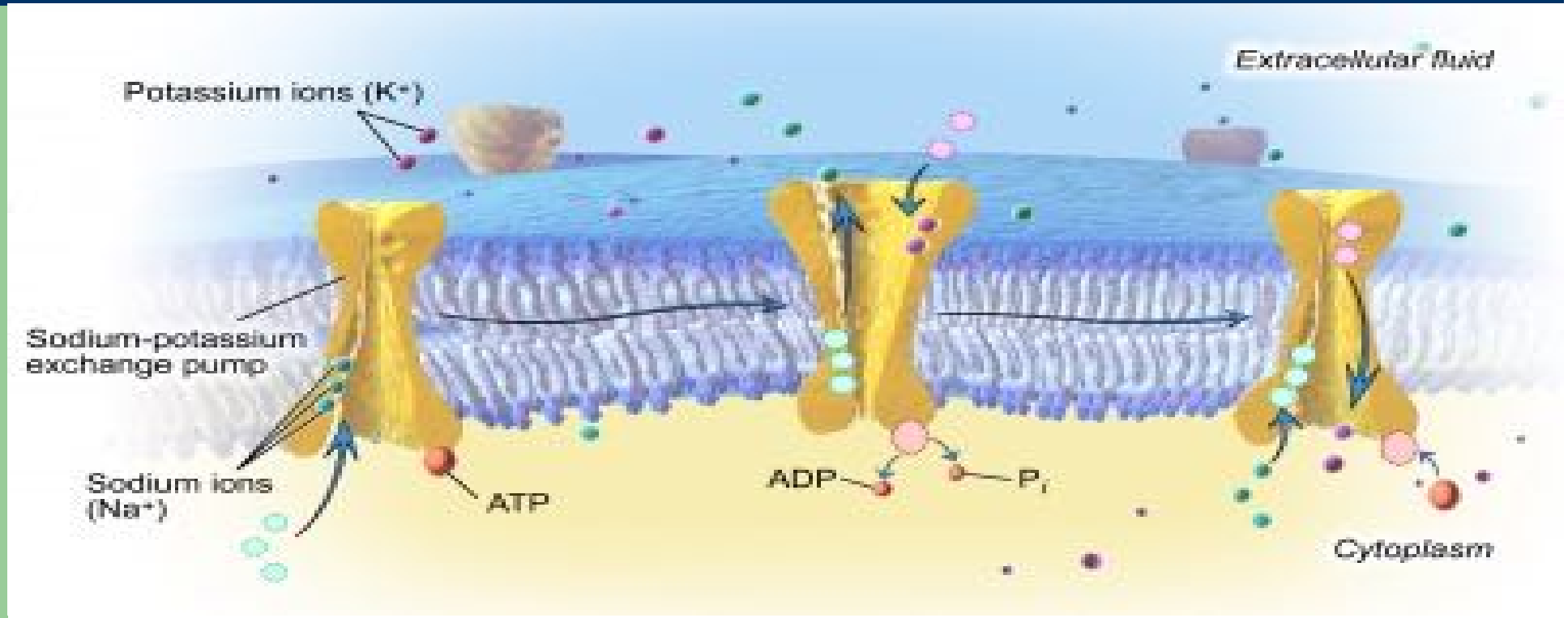
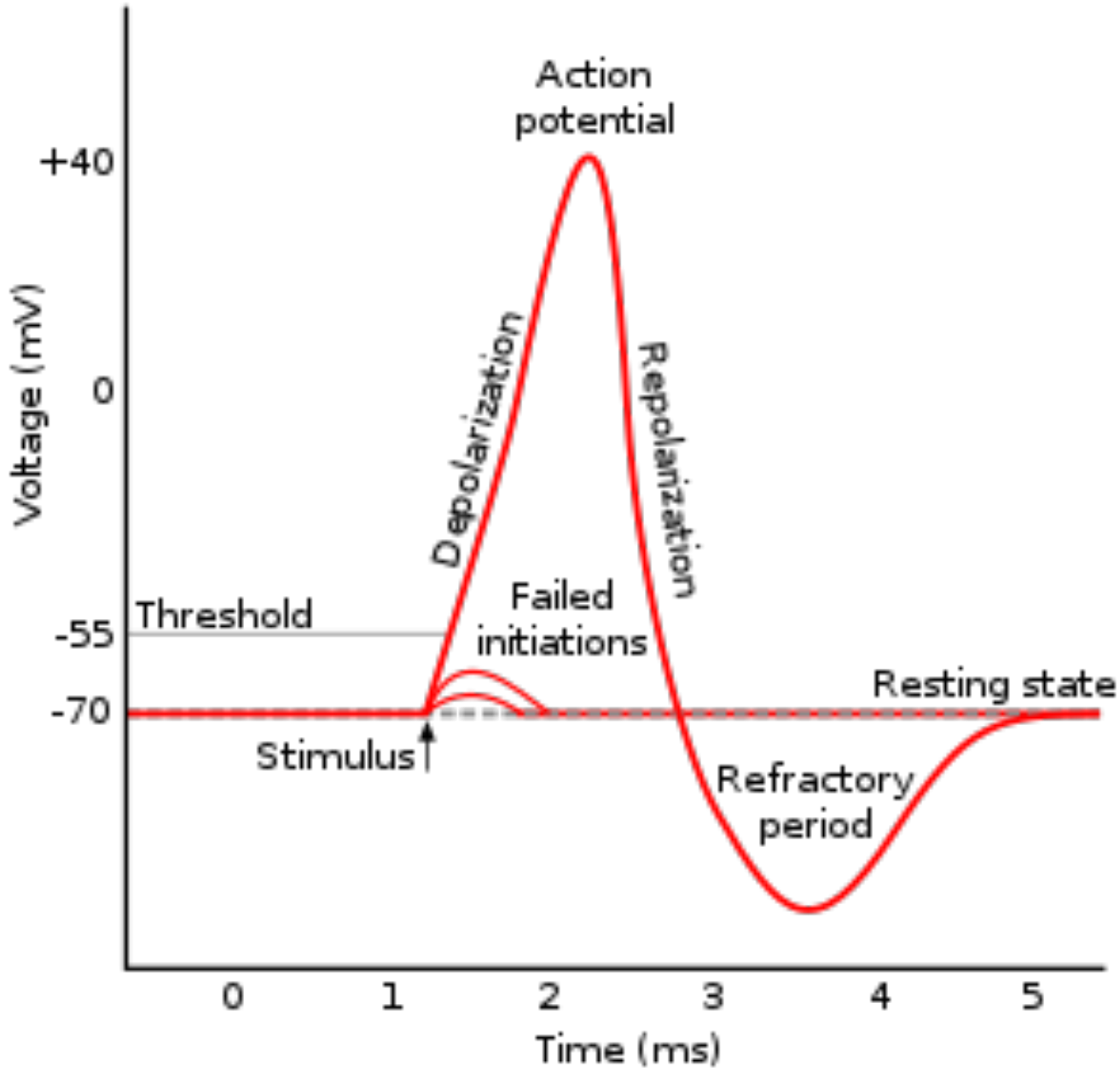

Namaste
مرحبا
Willkommen
Bem Vindo
Selamat Datang
Croeso
Bienvenue
Welcome
Bienvenidos
أهلا وسهلا
Benvenuti
Welkom
Bienvenue
Welcome
Bienvenidos
Croeso
Namaste
أهلا وسهلا
Selamat Datang
Welcome
Bienvenue
Bem Vindo
Willkommen
добре дошъл
Benvenuti
Willkommen
Benvenuti


Na+
Na+
3Na+
ATPase
K+
2K+
K+

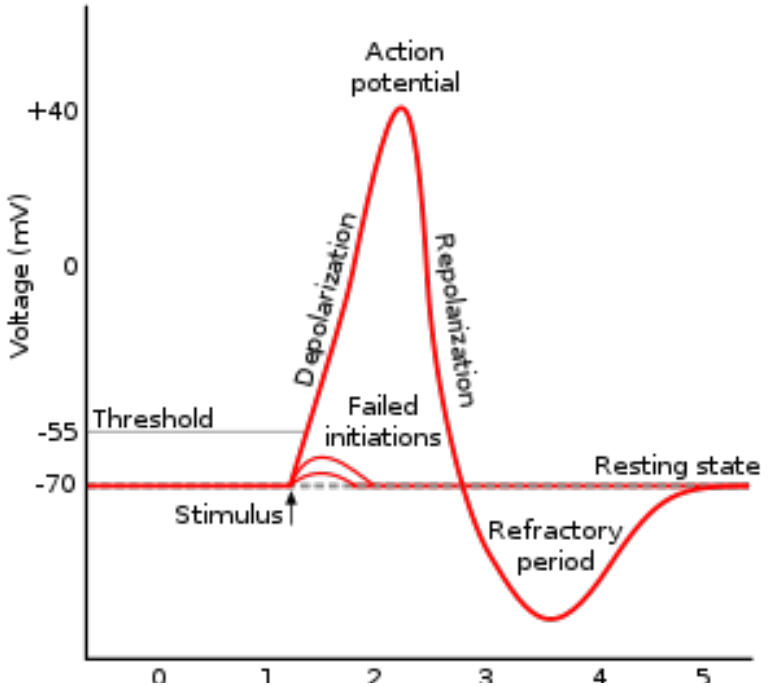

Extracellular fluid
Potassium ions (K+)
Sodium-potassium exchange pump
Sodium ions (Na+)
ATP
ADP
Pi
Cytoplasm

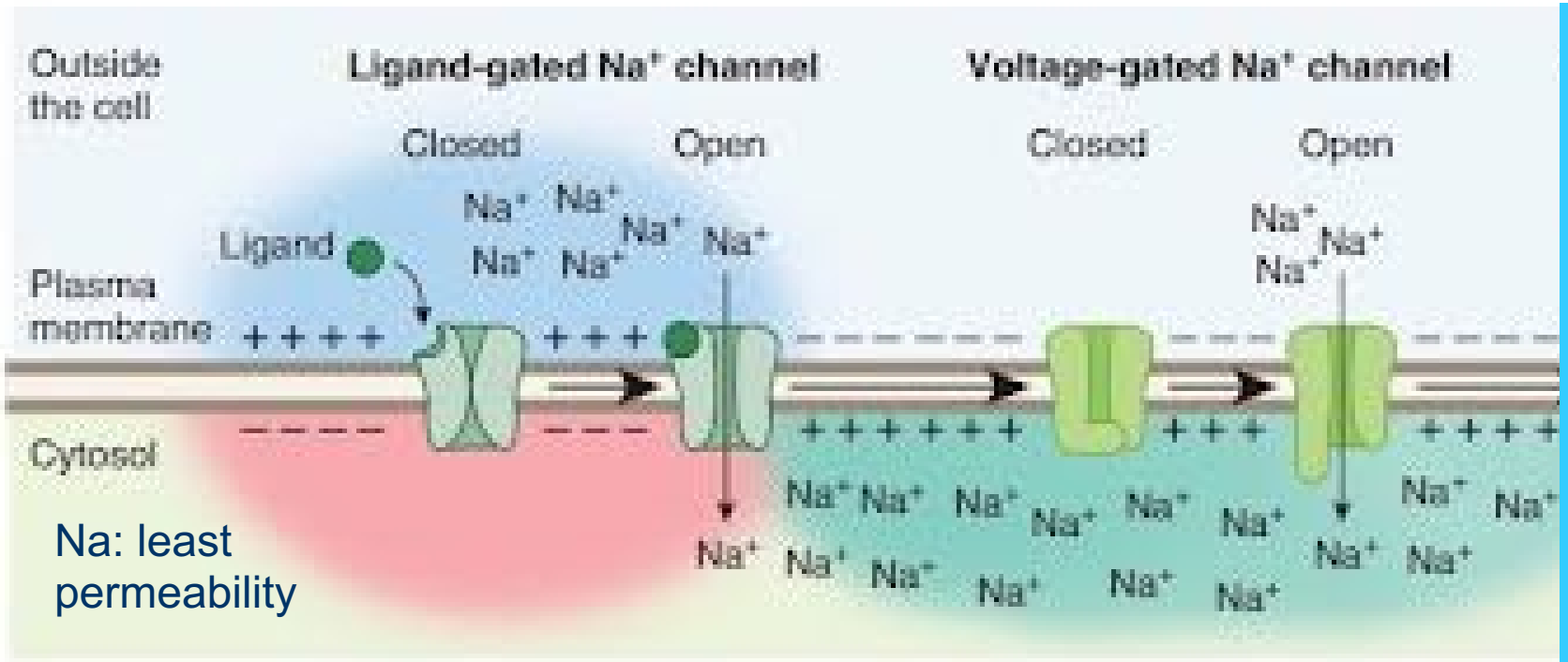

Action
potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed
initiations
Resting state
Stimulus
Refractory
period
0
1
2
3
4
5
Time (ms)

- **Na depolarisation**
- **K repolarisation**

Electrochemical concordance ➔ efflux

Then Na/K pump ➔ influx





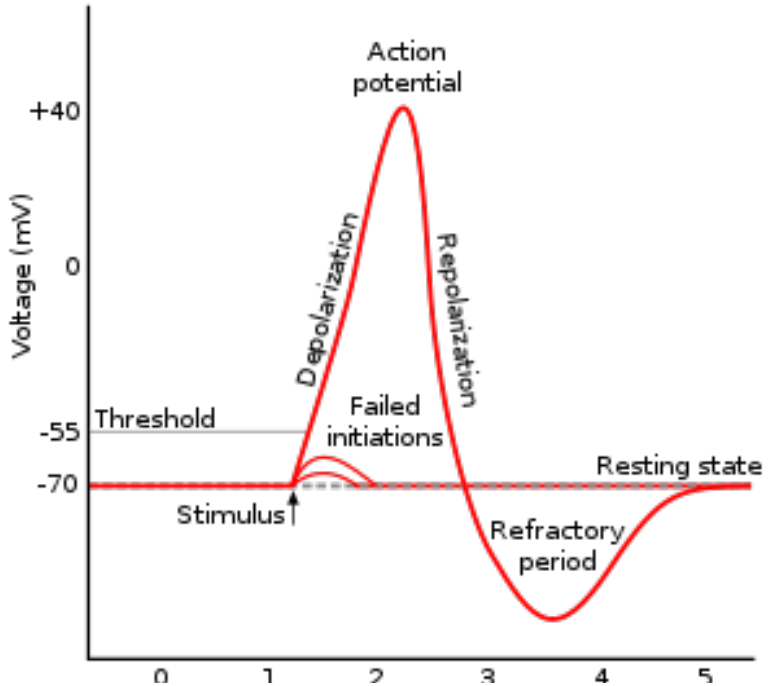
Na: least permeability

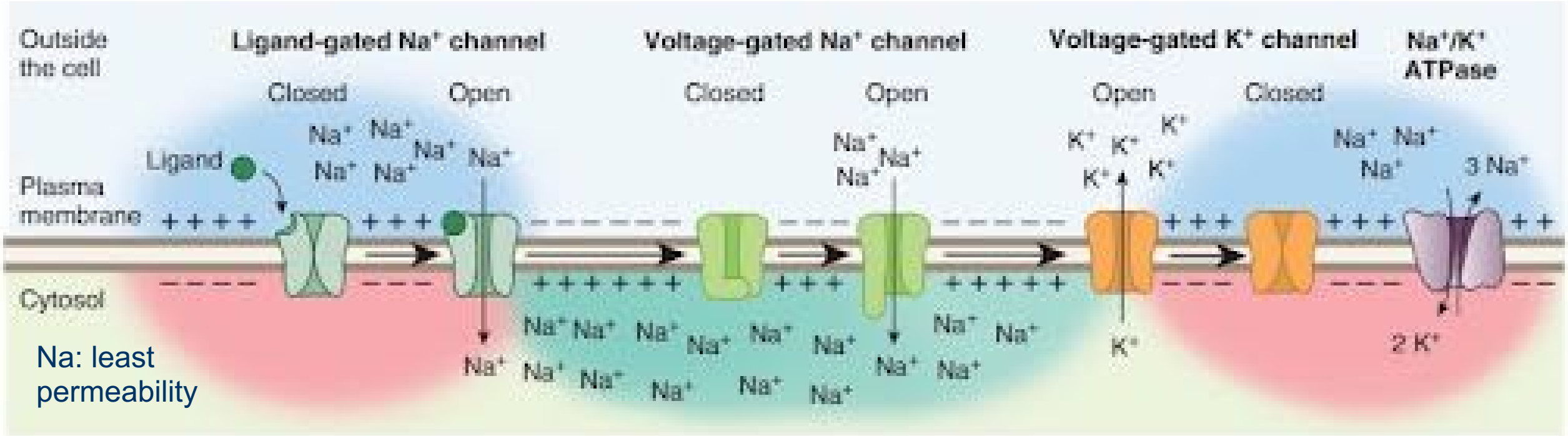
- **Calcium (slow) depolarisation**
- **Chloride (muscle) repolarisation**

Conc ➔ IN

Electric ➔ OUT (=in at -70mV)

↑ permeability ➔ stabilization effect





Na: least permeability

- **CHANNELS**

Passive ion pores

- **CO-TRANSPORTERS**

Symporters

Antiporters *(exchangers)*

- **PUMPS**

Active transporters (ATP)

Basolateral active Na/K exchange (most renal energy)

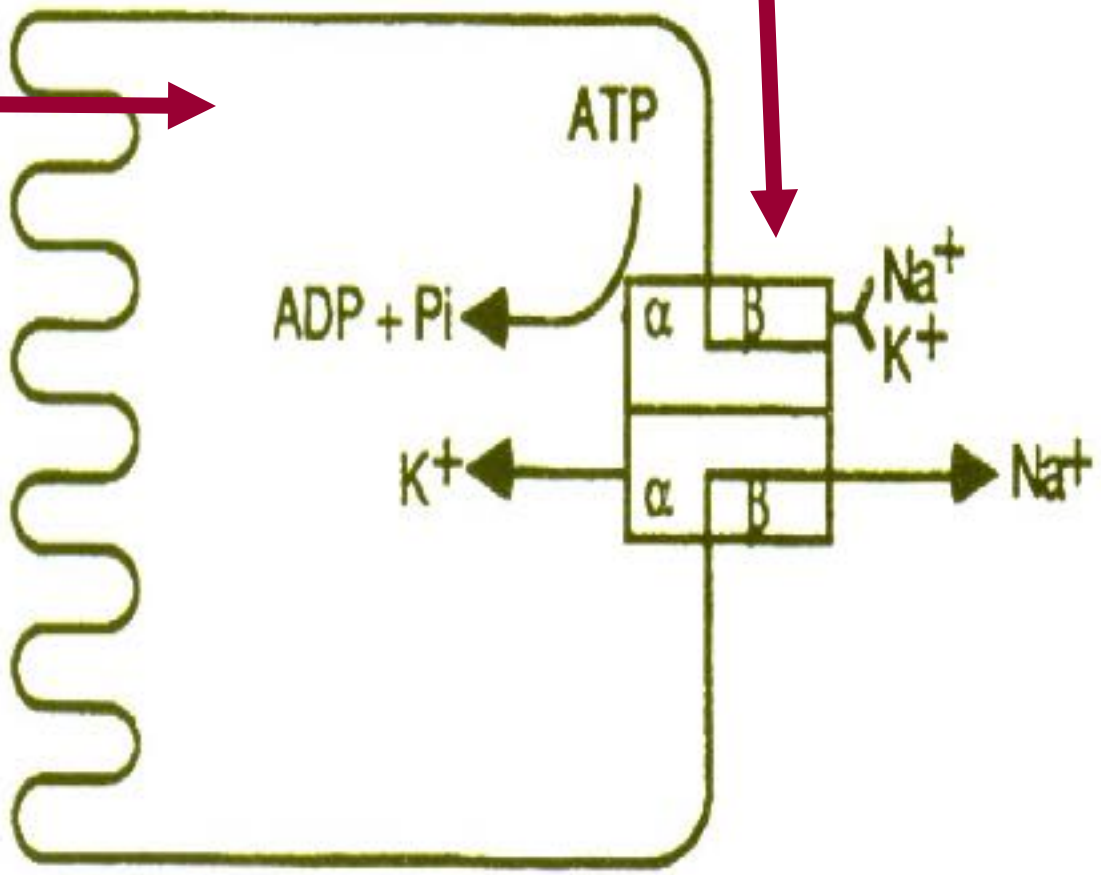
Apical Na transport

- Follows conc. gradient
- Secondary transporters

-Na coupled cotransport

-ENaC

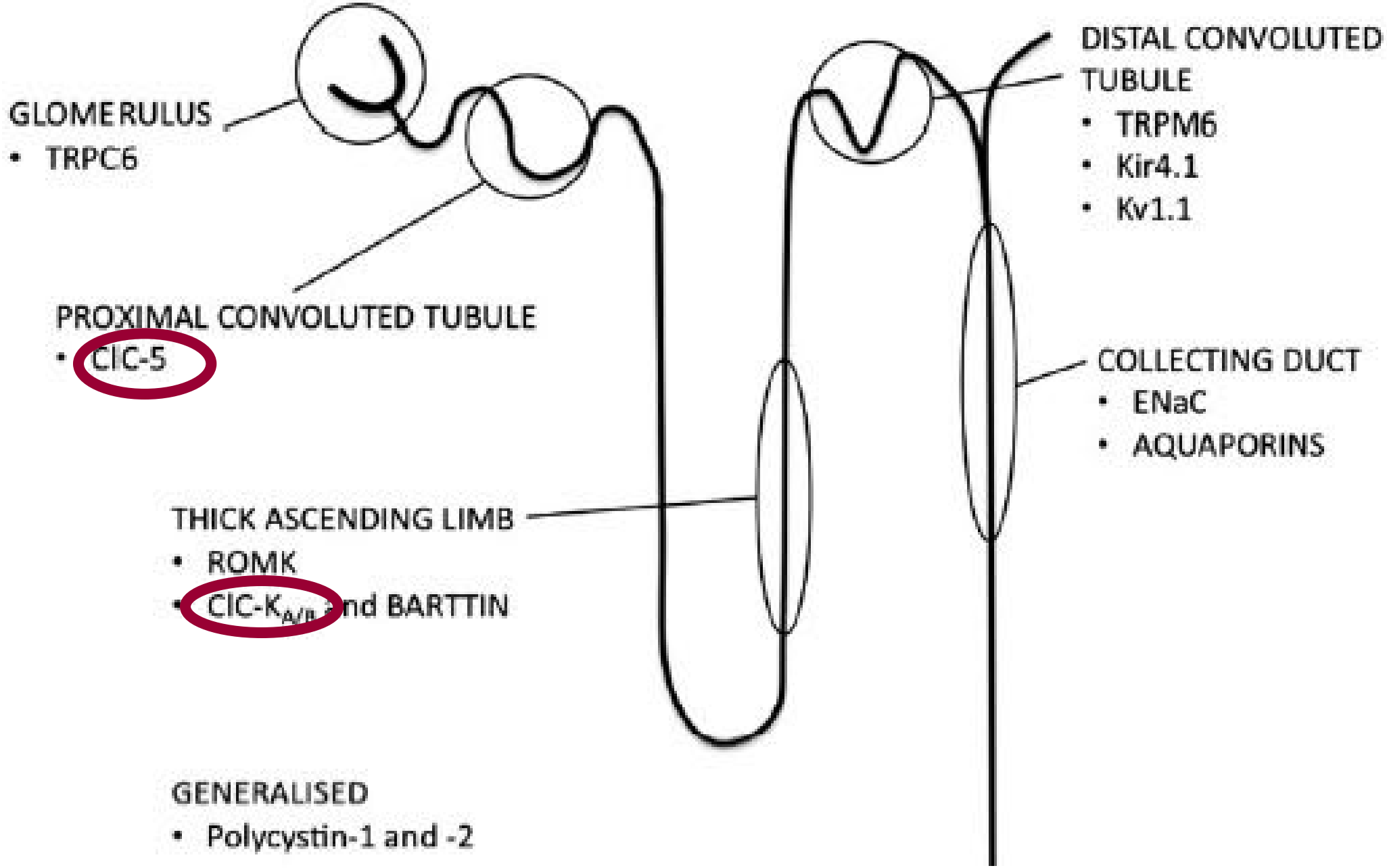
-Na/H exchanger



17

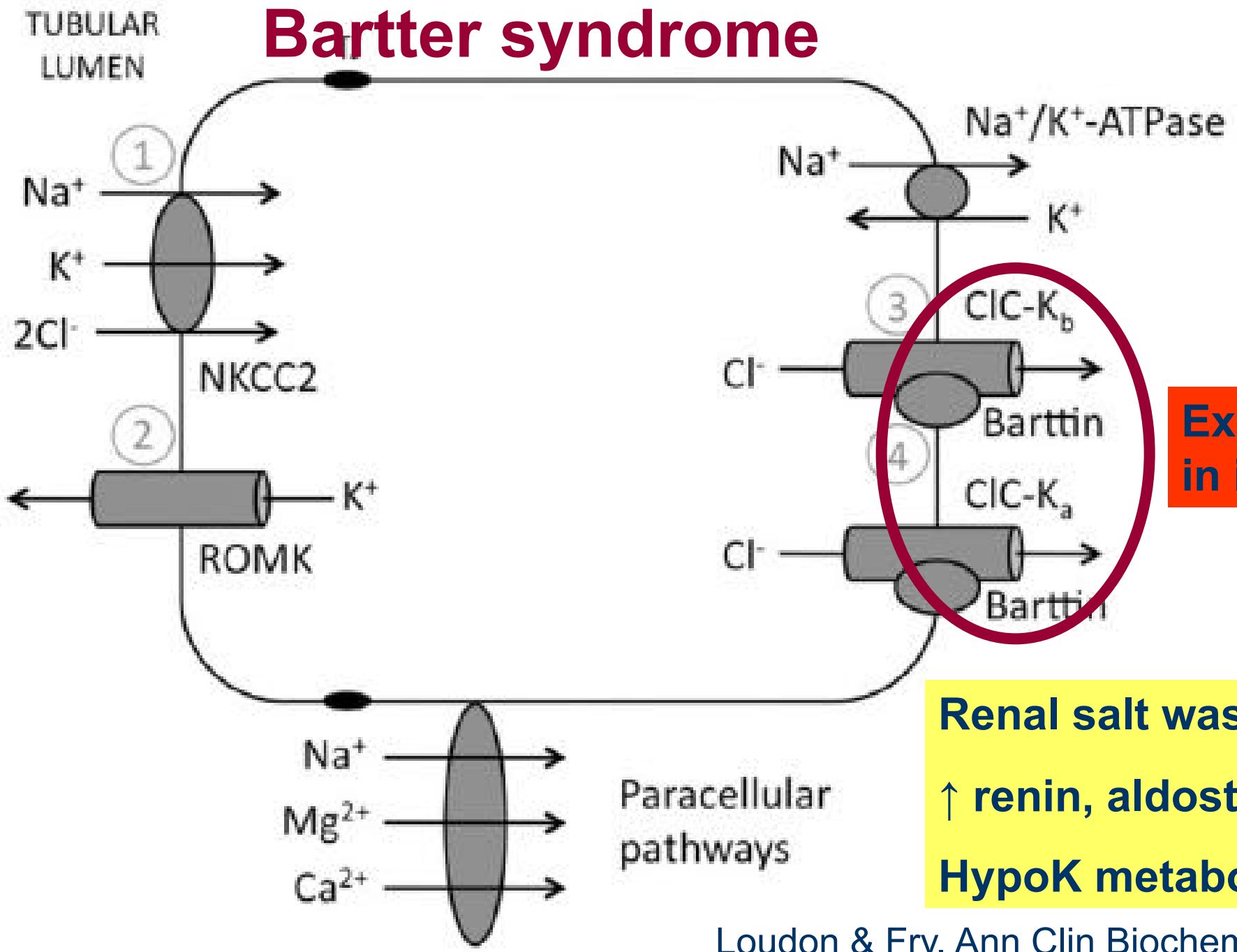
Cl^-

35.45



Loudon & Fry. Ann Clin Biochem. 2014

Bartter syndrome



Expressed in inner ear

Renal salt wasting

↑ renin, aldosterone

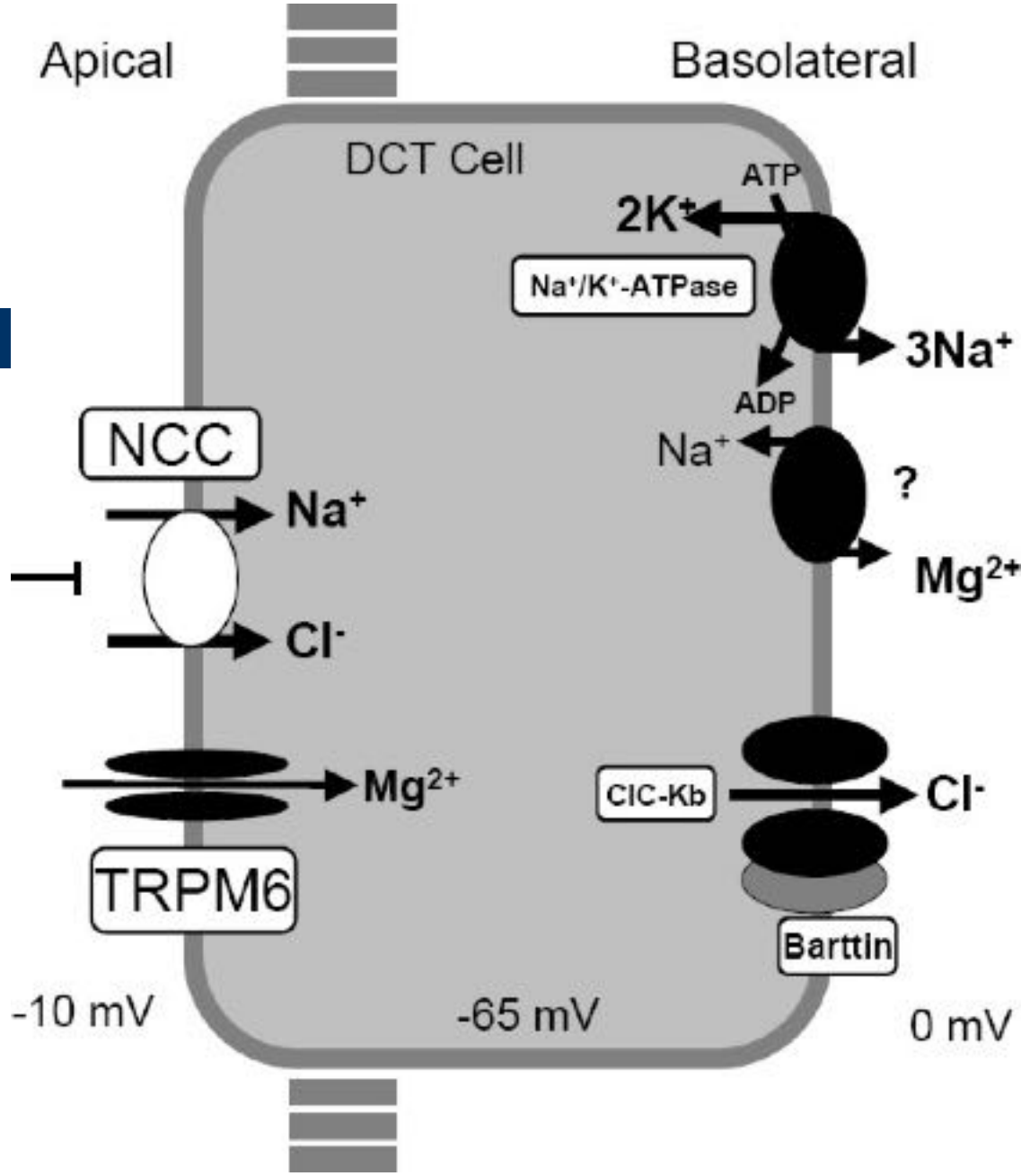
HypoK metabolic alkalosis

Loudon & Fry. Ann Clin Biochem. 2014

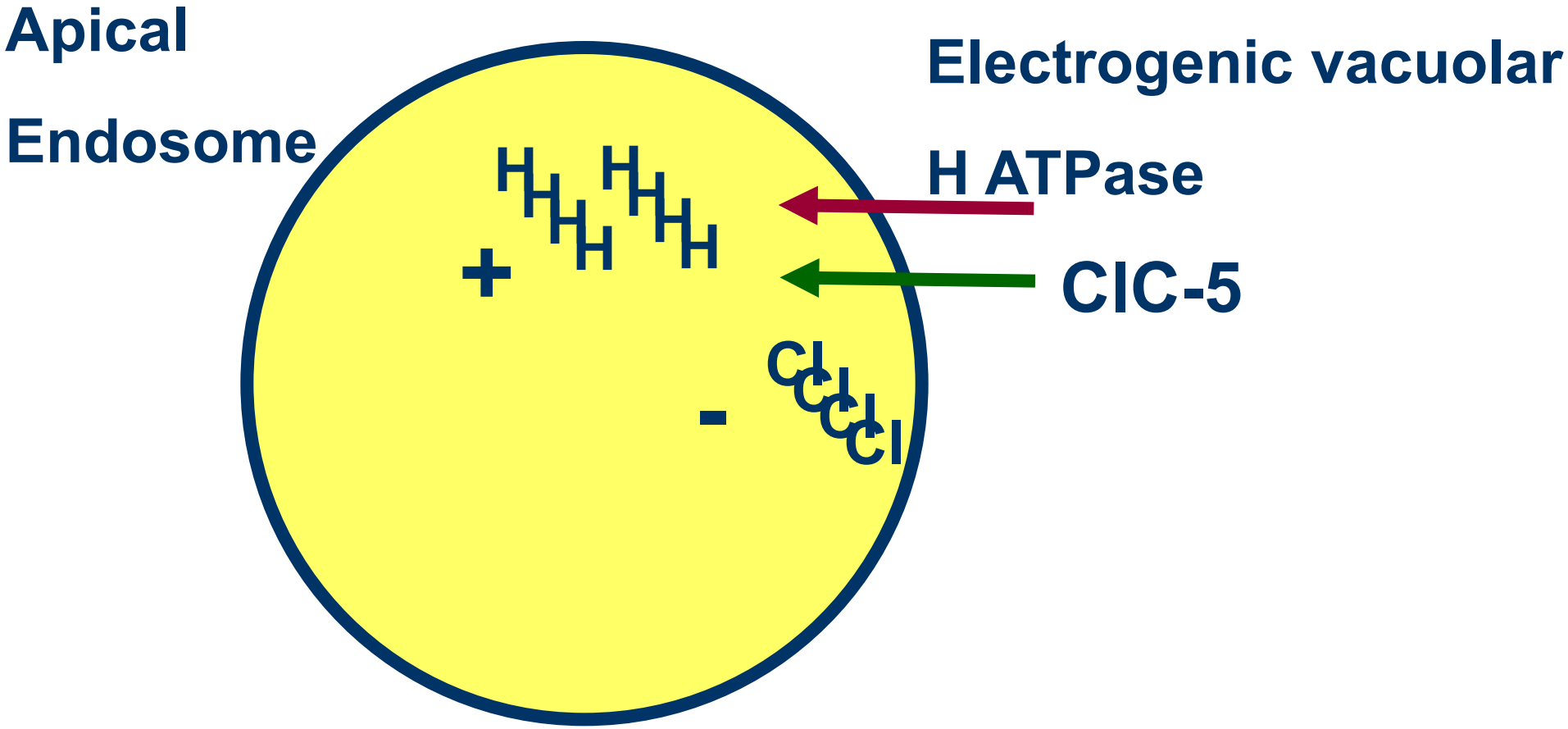
Gitelman syndrome

- **SLC2A3 mutation → NCCT**
  thiazide sensitive NaCl cotransporter
- **ClCNKB mutation → ClC-KB**

Na Cl Mg K (ALD) wasting
↓Mg → ↓Ca (PTH)



PCT receptor-mediated endocytosis



CIC-5

- Kidneys (mainly PCT) & Intestine
- Cl/H exchanger, apical endosomes
- Maintains acidification/ activation
- Cl dissipates high +ve intraluminal potential

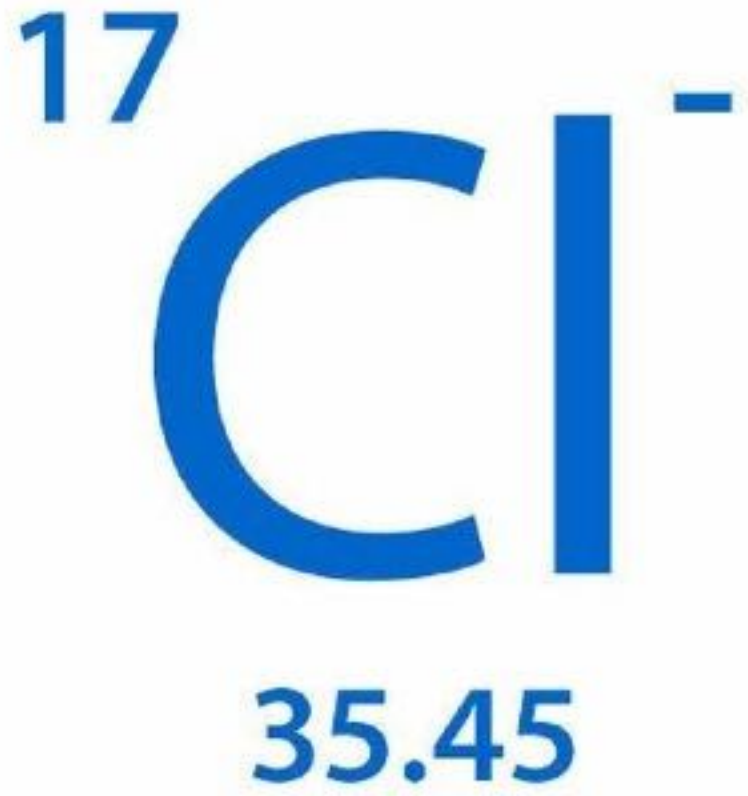
- *CLCN5* gene mutation → Dent's disease type I
- *OCRL1* gene mutation → Dent's disease type II
- . → Lowe syndrome

Inositol Polyphosphate-5-Phosphatase

Involved in regulating membrane trafficking

Numerous subcellular locations including endosomes & plasma membrane. May also play a role in primary cilium formation.

- **Electrical activity**
  - Voltage-gated
  - Ligand-gated GABA, Gly
- **Salt transport**
  - Renal
  - CFTR, , SLC26A3
- **Intracellular Cl/H exch. (organoids)**
  - Dent
  - Storage



EXTRA-RENAL

- **Electrical activity**
  - Voltage-gated
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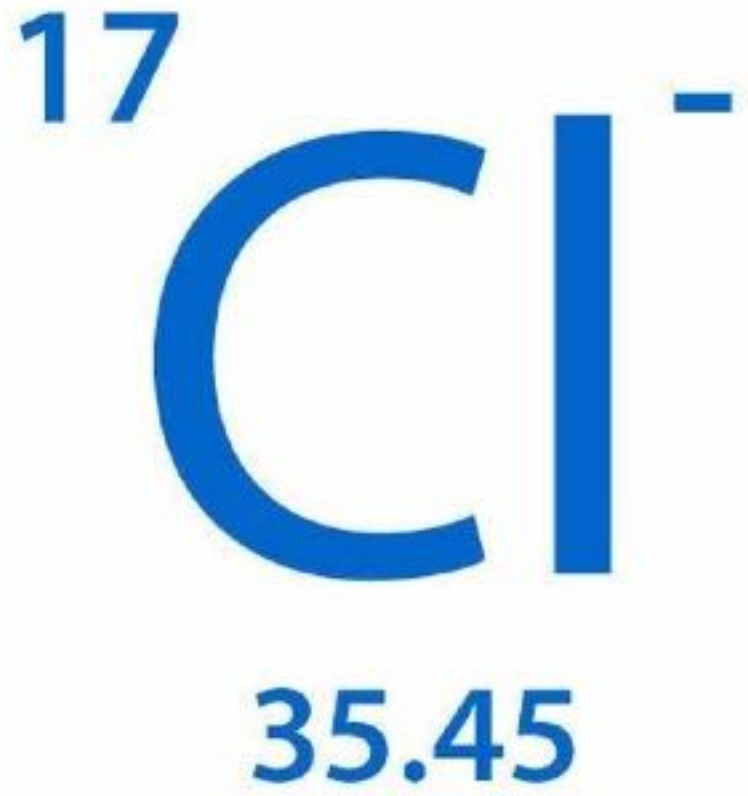


Voltage-gated ClC-0 cloned (1990)

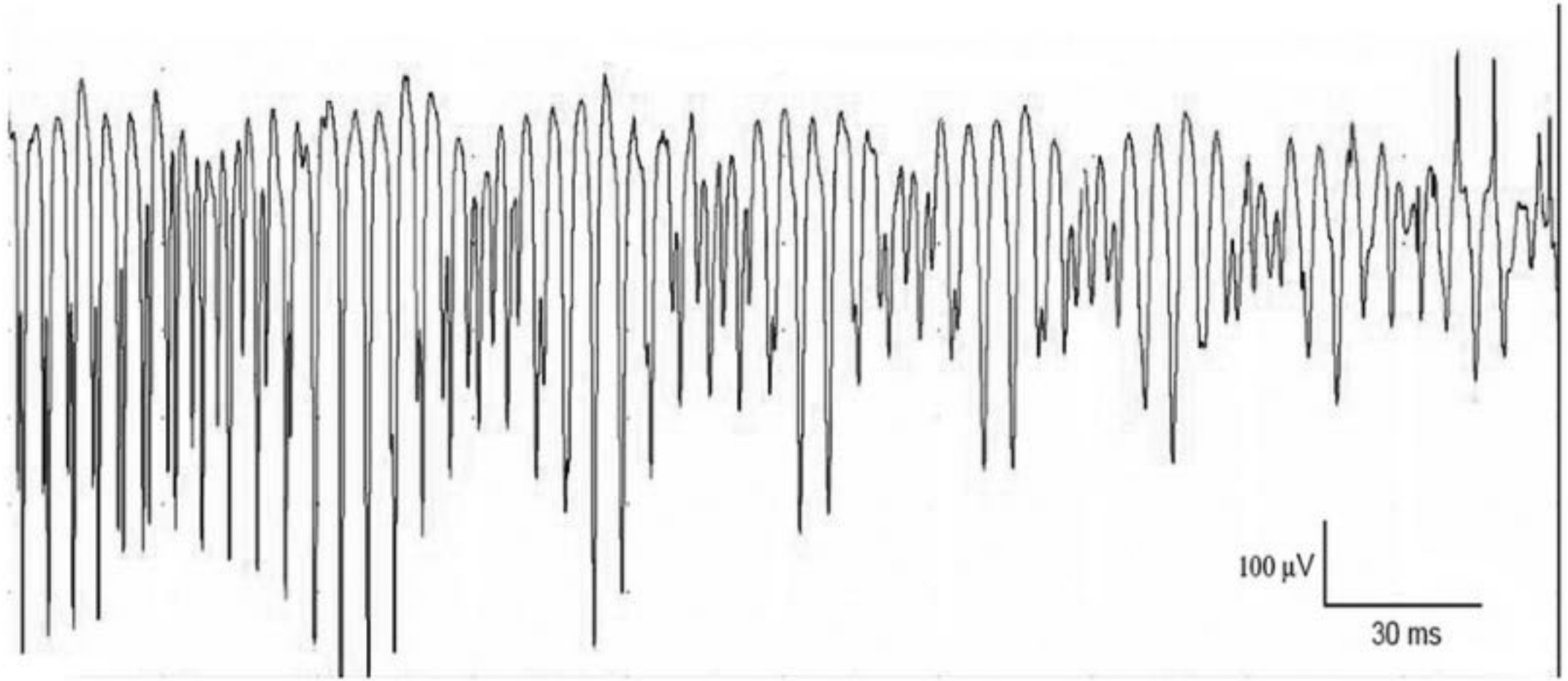
➔ ***ClCN genes coding ClC proteins***

-Plasma membrane channels

-Cl/H exchangers ***NOT strictly channelopathies***

- Torpedo marmorata

Myotonia



Myotonia congenita

AD Thomsen

AR Becker

- **Chloride (muscle) repolarisation**

Conc ➔ IN

Electric ➔ OUT (=in at -70mV)

↑ permeability ➔ stabilization effect

- **ClC1 in skeletal muscle**
- **Voltage-gated Cl channel**
- **Repolarisation & stabilization**

Ligand-gated Cl channelopathies

CIC-2

- CNS: GABA-A receptors ➔ ↑ intracellular Cl ➔ Inhibitory

  Proposed relation to epilepsy (3q26)
- Widely expressed

  Unproven relation to lung development, gastric secretion
- Mice: *leukoencephalopathy, blindness, testicular degeneration*

Ligand-gated Cl channelopathies

Hereditary hyperekplexia (stiff baby syndrome)

- ↑ startle response to mild stimuli (visual, aud., tactile)
- Hypertonia (during no voluntary movement possible)
- Laryngospasm, apnea may occur. ?SIDS
- Glycine-mediated (GLRA1 mutation)

EXTRA-RENAL

- **Electrical activity**
  - Voltage-gated
  - Ligand-gated GABA, Gly
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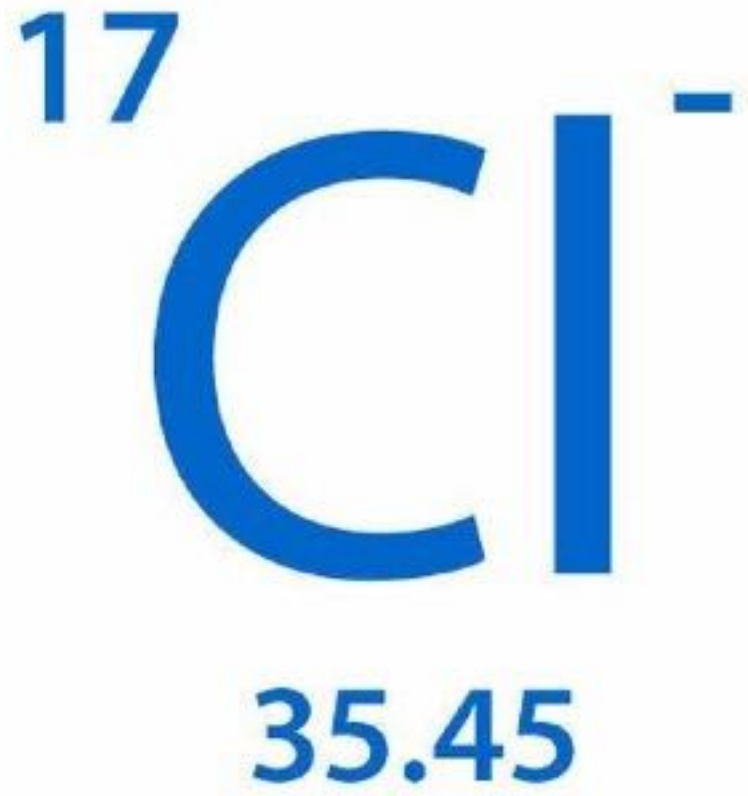
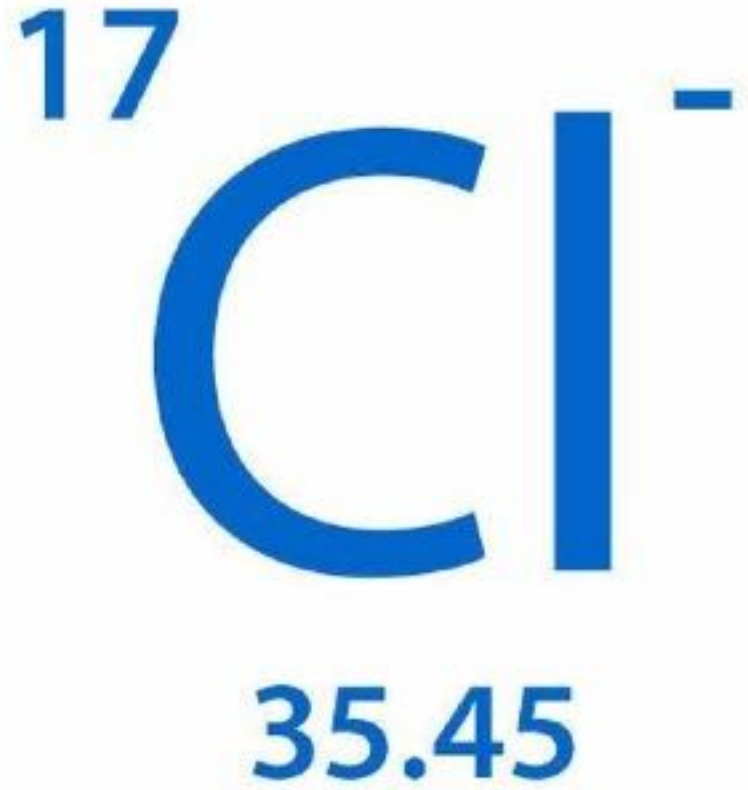


CIC-7

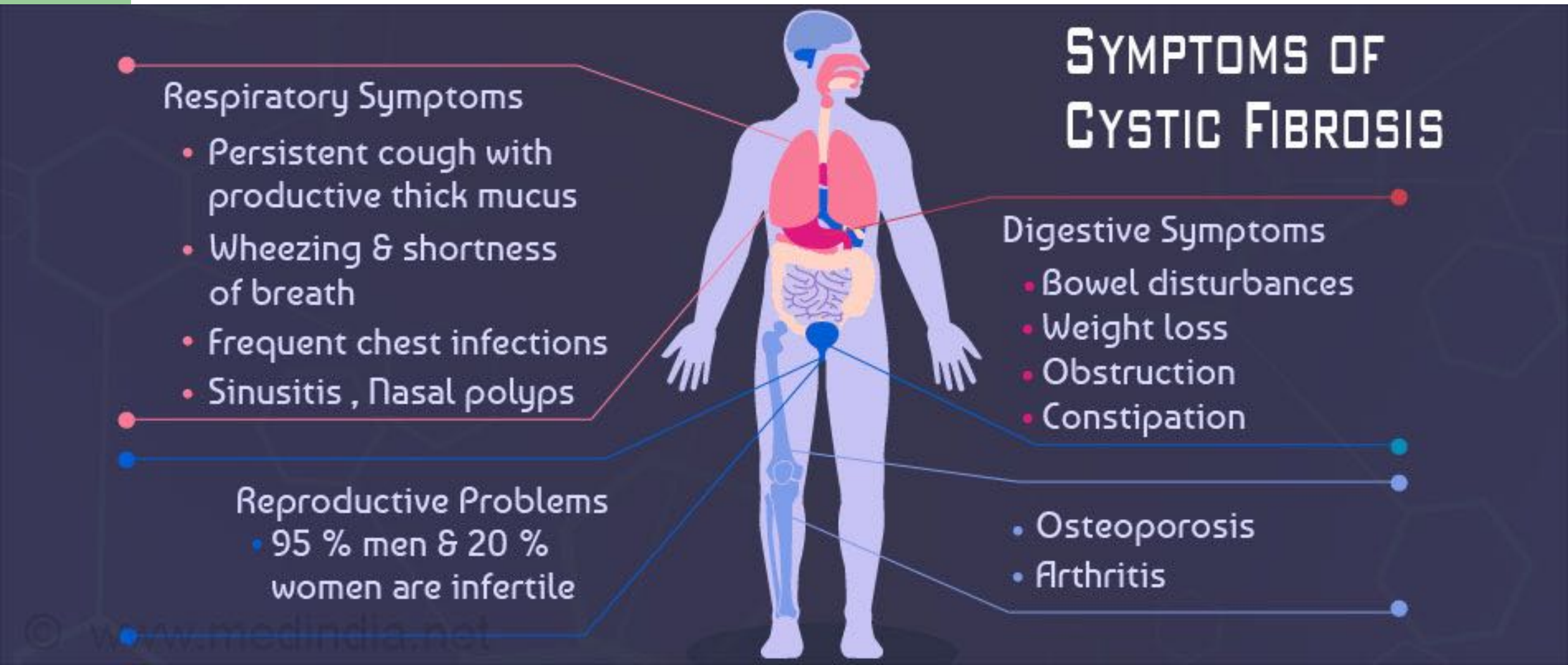
- Widely expressed, lysosomes
- Osteopetrosis (polymorphisms BMD)
- Lysosomal storage & neurodegeneration
- Retinal degeneration

EXTRA-RENAL

- **Electrical activity**
  - Voltage-gated
  - Ligand-gated GABA, Gly
- **Salt transport**
  - Renal
  - CFTR, SLC26A3
- **Intracellular Cl/H exch. (organoids)**
  - Dent
  - Storage



CFTR

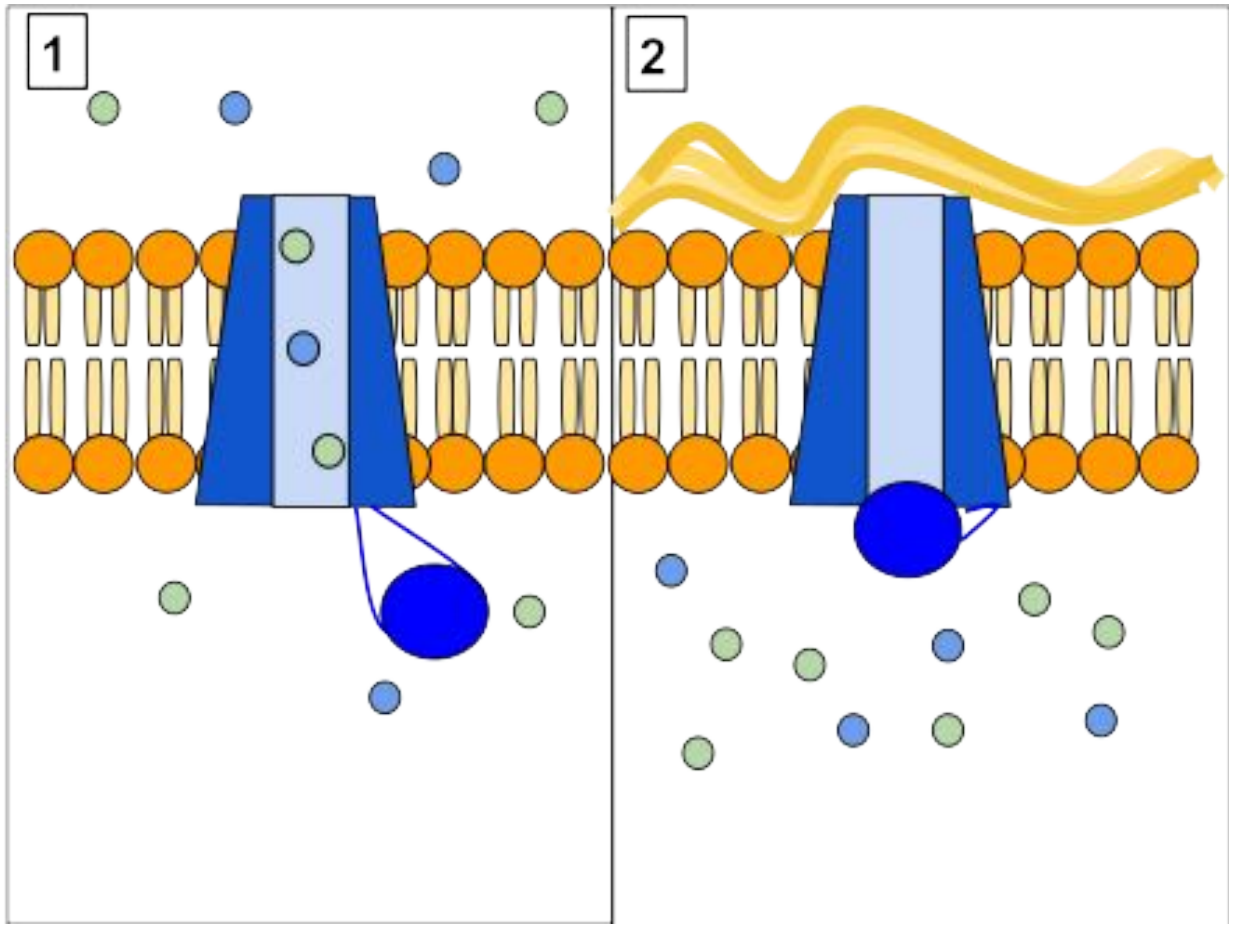

Symptoms of Cystic Fibrosis
Respiratory Symptoms
• Persistent cough with productive thick mucus
• Wheezing & shortness of breath
• Frequent chest infections
• Sinusitis , Nasal polyps
Digestive Symptoms
• Bowel disturbances
• Weight loss
• Obstruction
• Constipation
Reproductive Problems
• 95 % men & 20 % women are infertile
• Osteoporosis
• Arthritis
© www.medindia.net

C F Transmembrane (conductance) Regulator

Phosphorylation-dependent (cAMP) apical Cl channel

- The most common hereditary lethal disease in Caucasians (1:3000)
- Abnormal epithelial salt/ water transport
- ENaC dys(up)regulation
- Resp., enterocytes, gland acini, pancreas, vas deferens, …

CFTR (lung ionocytes)



Abnormal CFTR allows Cl influx but not efflux

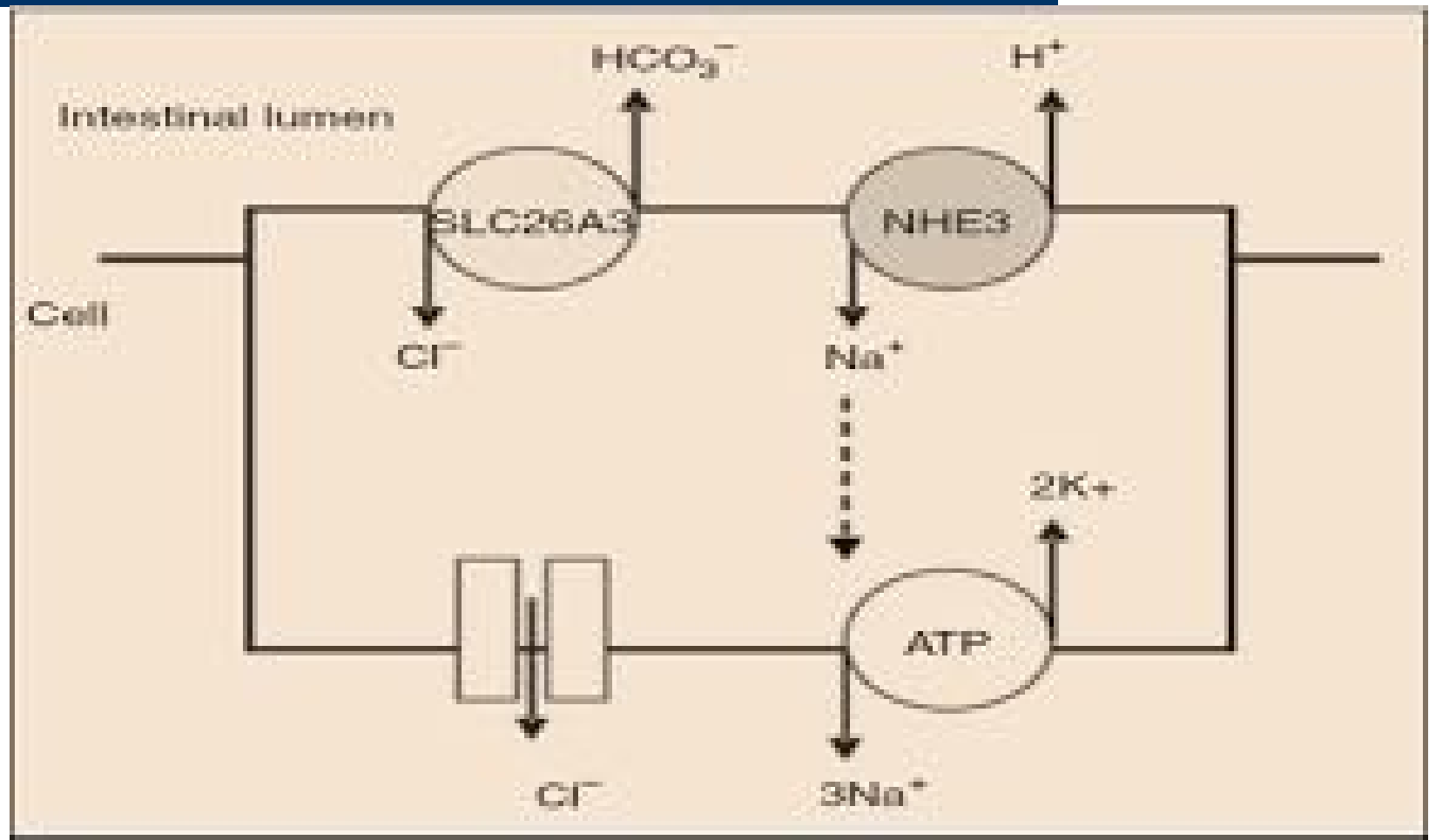
↓ Cl, Na, H_2O in secretions

Congenital Chloride (losing) Diarrhea

- Solute linked carrier

SLC26A3

Membrane anion exchanger



Congenital Chloride (losing) Diarrhea

- Solute linked carrier SLC26A3

  Membrane anion (Cl/HCO3 exchanger)
- Watery diarrhea with low pH & high Cl content
- Hypochloremic metabolic alkalosis

BUTYRATE:

↑ intestinal water and ion absorption through a variety of mechanisms, including the activation of a parallel Cl-/butyrate and Na+/H+ exchanger.

New targeted therapies may be under way….

- **Mexiletene & Lamotrigine:** Voltage-gated Na channel blockers. Proposed for myotonia.
- **Targets F508 deletion in CF:**

  The newly approved medication combines two “corrector” molecules (elexacaftor and tezacaftor) that address protein misfolding plus a “potentiator” (ivacaftor) that improves chloride channel opening.

CONCLUSION

- Don’t overlook anions
- Chloride transport:
  - Salt & water reabsorption
  - Epithelial salt & water transport
  - Electrical activity
  - Endosome & Lysosome function
- There’s a lot we don’t know

Thank you

Q1

Under basal (resting) conditions, the net movement of chloride ions across the cell membrane is

A zero

B inwards according to concentration gradient

C outwards according to electrical gradient

D outwards by active transport

Q2

Disorders of chloride channels/ chloride transport are implicated in the following conditions EXCEPT

A Bartter syndrome

B Nephrogenic diabetes incipidus

C Myotonia congenita

D Cystic fibrosis

Q3

The main mechanism of proteinuria in Dent disease is

A the presence of abnormal proteins in plasma

B increased glomerular permeability

C impaired tubular reabsorption

D losses from the urinary tract