UNIVERSITY OF BASRAH
AL-ZAHRAA MEDICAL COLLEGE

Ministry of higher Education
and Scientific Research

MEMBRANES AND RECEPTORS MODULE

Academic year 2025-2026/ S3

SESSION: 2

LECTURE: 2 DURATION: 1hr

ATP-DEPENDENT ION PUMPS AND ION EXCHANGERS

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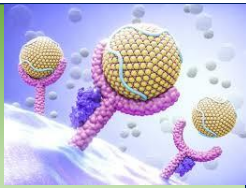
John E. Hall and Michael E. Hall. Guyton and Hall Textbook of Medical Physiology, 14th Edition, Elsevier, Philadelphia, 2021, ISBN978-0-323-67280-1.
Koeppen, B.M. & Stanton, B.A. Berne & Levy: Principles of Physiology, 7th Edition, Philadelphia, PA, 2018, ISBN: 978-0-323-39394-2.



Learning Objectives (LO):

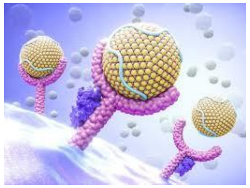
Outline the major physiological roles of: (LO1):

- Sodium-potassium ATPase (Na^+/K^+-ATPase, Na^+ pump).
- Plasma membrane Ca^{2+}-ATPase (PMCA).
- Sarcoplasmic/endoplasmic reticulum ATPase (SERCA).
- Sodium hydrogen exchange (NHE).
- Sodium calcium exchange (NCX).
- Anion exchange (AE).

- **How do ion transporters work together in cell physiology? (LO2)**

To consider how ion transport contribute to: (LO3)

- Cellular Ca^{2+} handling?
- Cellular pH regulation?
- Cell volume regulation?
- Renal bicarbonate reabsorption?
- Renal Na^{+} handling?

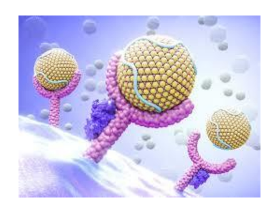


LO1

Chemical compositions of extracellular and intracellular fluids **(Ion gradients across the plasma membrane)**

ECF	
Cations:	**Anions:**
Na^+ (142mmol/L)	**Cl^-** (108mmol/L)
K^+ (4.2mmol/L)	**HCO_3^-** (24mmol/L)
Mg^{2+} (0.8mmol/L)	

ICF	
Cations:	**Anions:**
Na^+ (14mmol/L)	Cl^- (4mmol/L)
K^+ (140mmol/L)	HCO_3^- (10mmol/L)
Mg^{2+} (20mmol/L)	**Phosphate ions**



LO1

Ion gradients are maintained across the plasma membrane by activity of:

ATP-dependant ion pumps

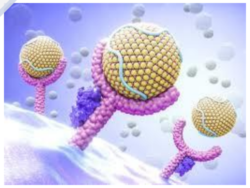
(Energy drives from hydrolysis of ATP)

- Na^+/K^+-ATPase
- Plasma membrane Ca^{2+}-ATPase (PMCA)
- Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA)

Ion exchangers

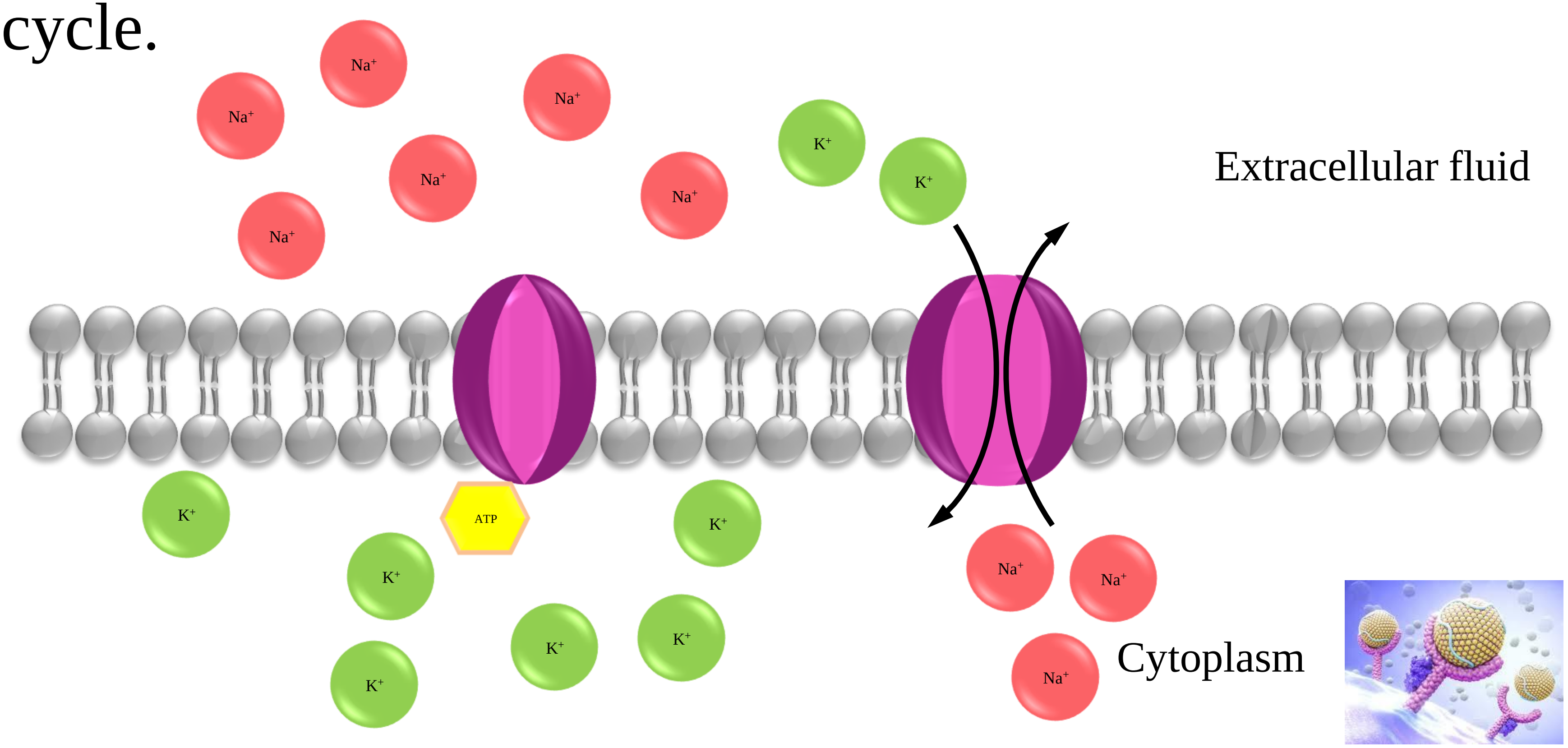
(The energy drives from difference in ion gradient).

- Na^+/Ca^{2+} exchanger
- Na^+/H^+ exchanger
- Sodium-independent anion exchanger (Cl^-/HCO_3^- exchanger)



Na^+/K^+-ATPase (Na^+/K^+ pump)

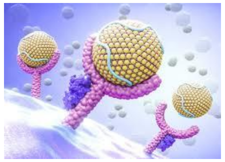
- Found in the plasma membrane of all cells.
- Energy is derived directly from breakdown of ATP.
- 3 Na^+ are exported and 2 K^+ are imported. Then, there is a net export of a single positive charge per pump cycle.



- The action of the Na^+/K^+ ATPase is the most important example of **primary active transport**.

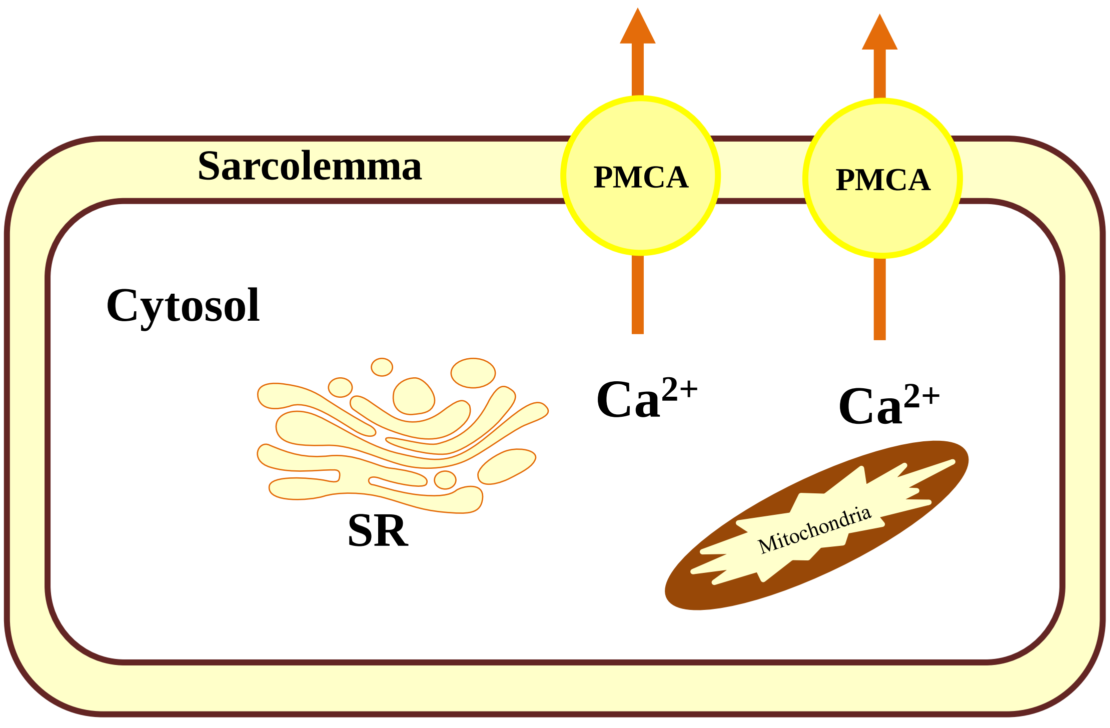
- Drives many secondary active transport processes

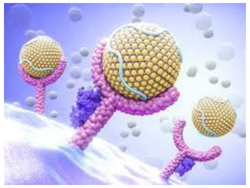
  - **Ion homeostasis**
  - **$[Ca^{2+}]_I$**
  - **pH_i**
  - **Cell volume**
  - **Nutrient uptake**
  - **Resting membrane potential**



Plasma membrane Ca^{2+} ATPase (PMCA)

- Ca^{2+} effluxes to the extracellular fluid is carried out by PMCA.
- The pump is powered by the hydrolysis of ATP.

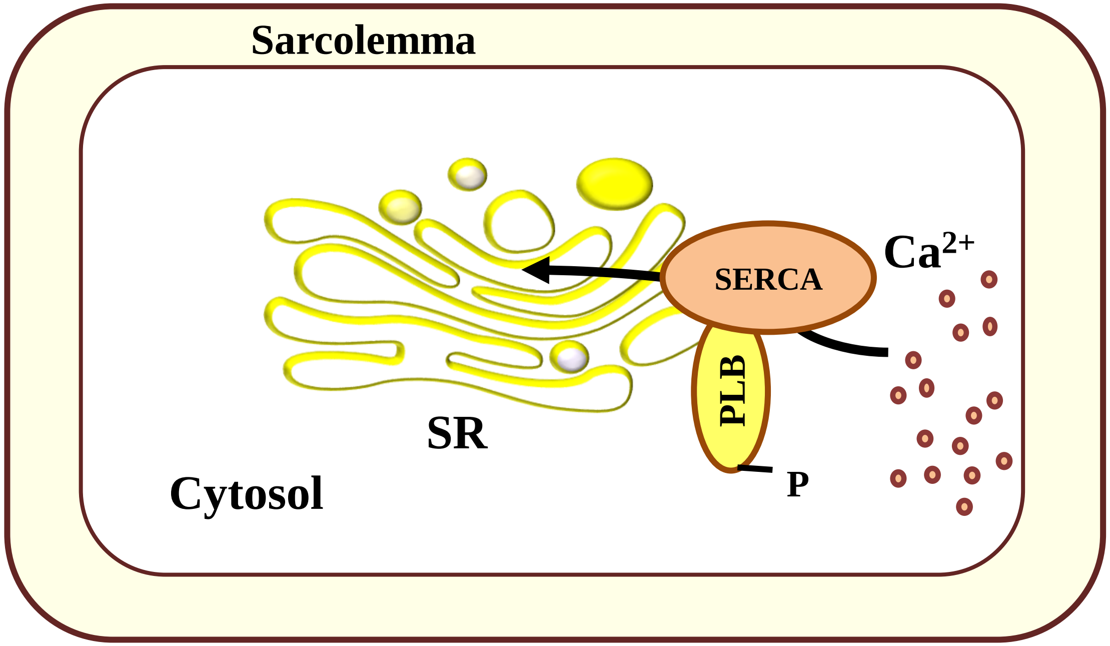


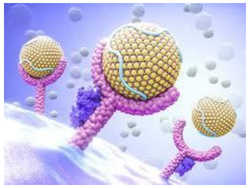


Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA)

LO1

- SERCA resides in the SR within muscle cells.
- Ca^{2+} is transferred from the cytosol of the cell to the lumen of the SR by Ca^{2+} ATPase at the expense of ATP hydrolysis.

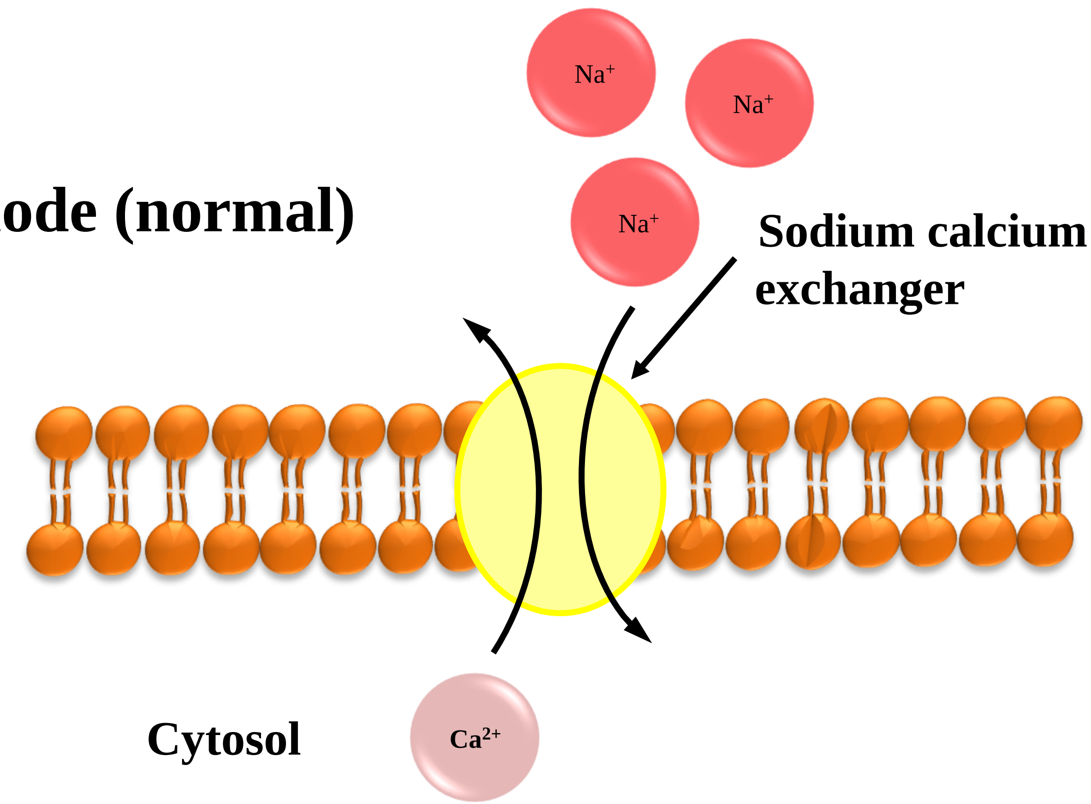


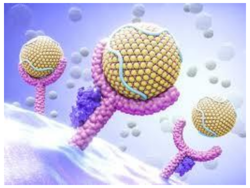


Sodium calcium exchanger (NCX)

- NCX is a carrier for Ca^{2+} which couples the movement of Na^{+} and Ca^{2+} in the opposing directions (3 Na^{+}: 1 Ca^{2+}).

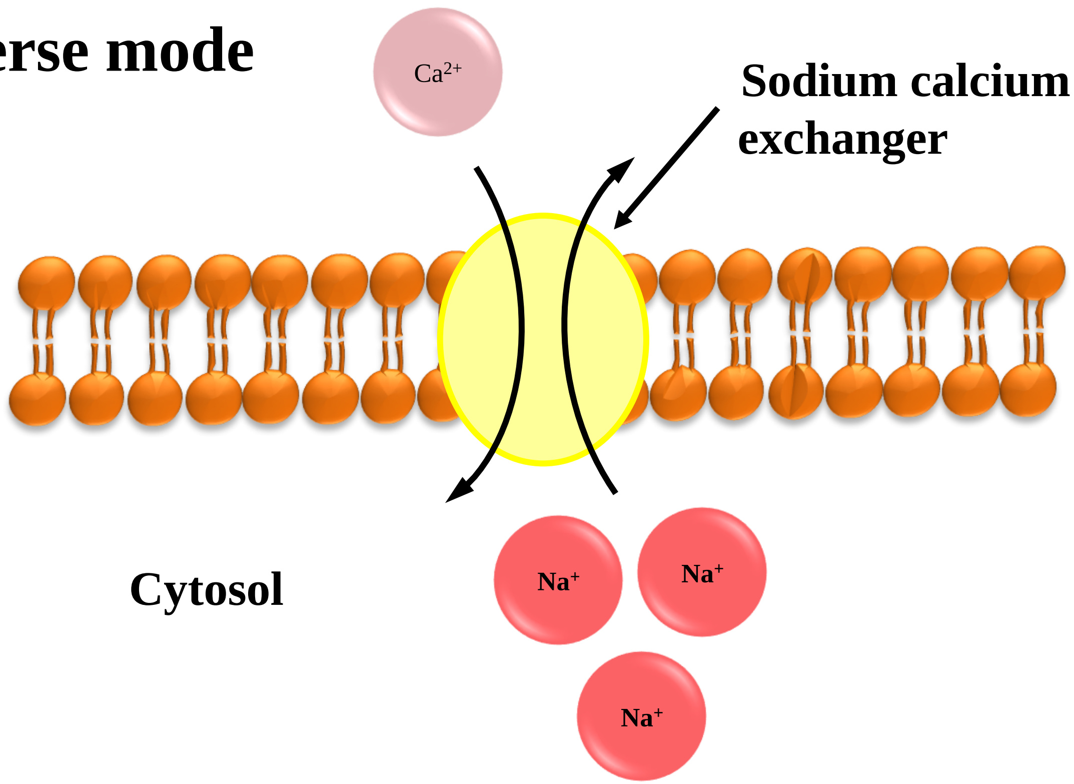
  - **Forward mode (normal)**

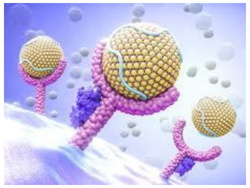




Sodium calcium exchanger (NCX)

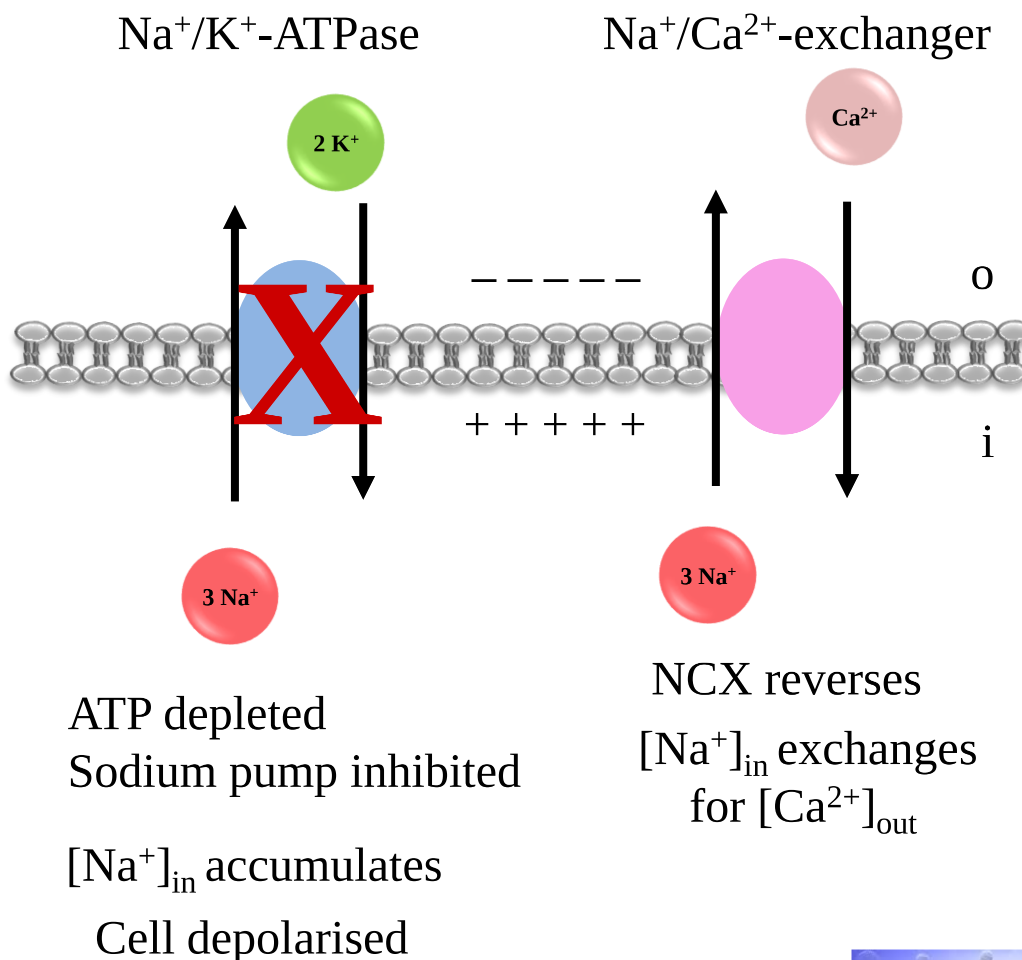
- **Reverse mode**

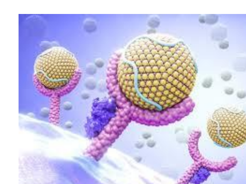




Sodium calcium exchanger (NCX) in ischaemia

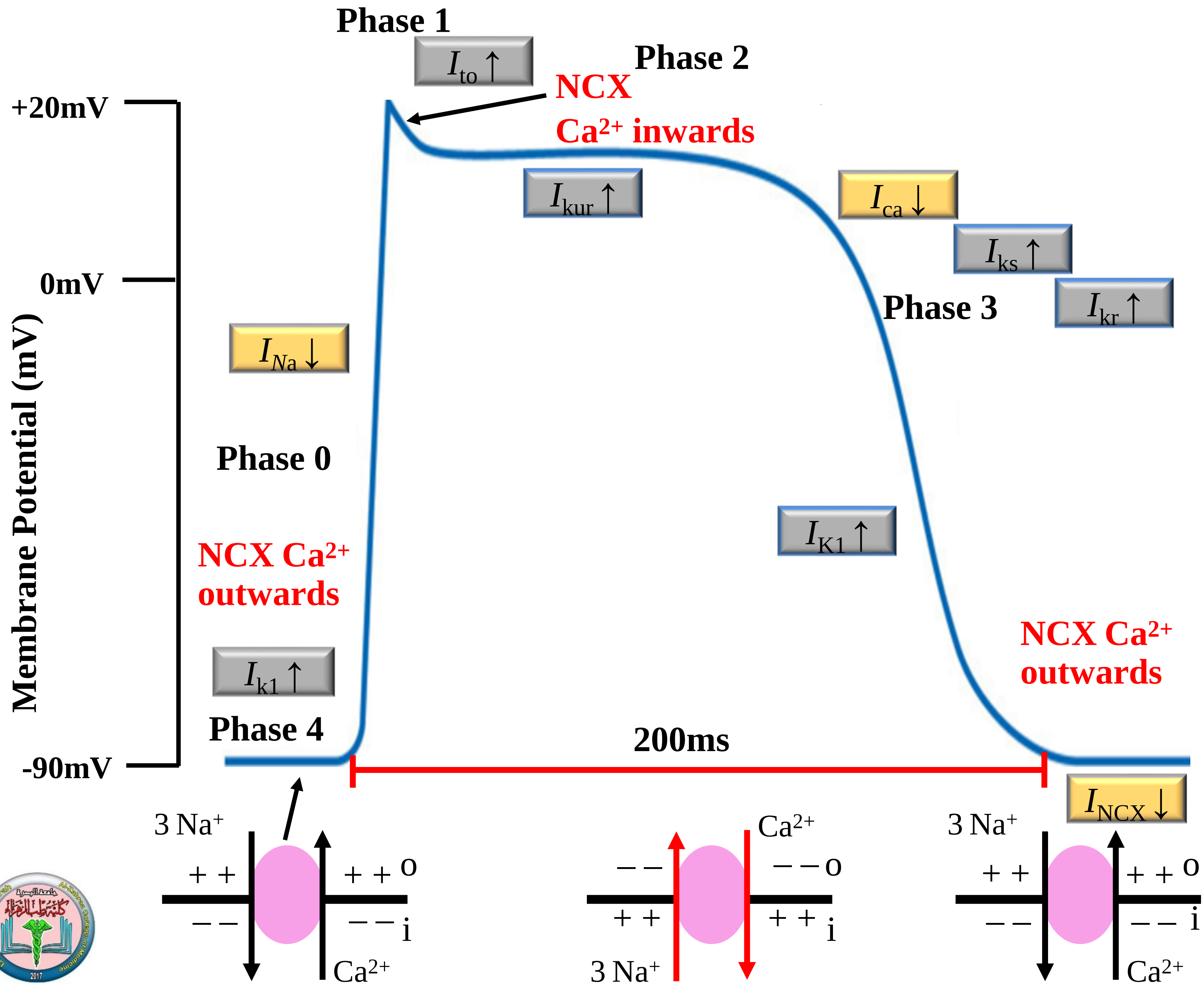
- NCX can reverse and transport Ca^{2+} into the cell.
- Na^+/K^+-ATPase is inhibited during ischaemia.

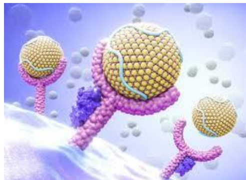




NCX in ventricular cardiomyocytes

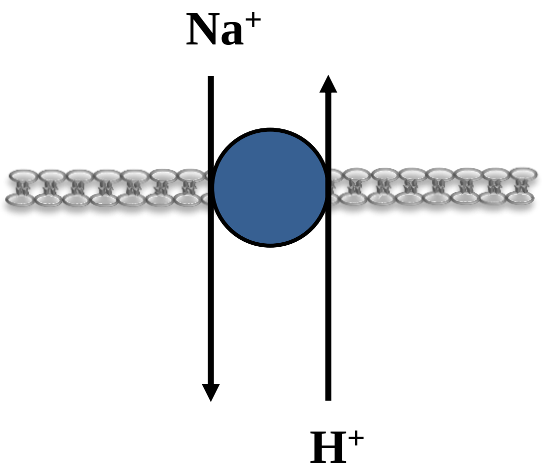
LO1

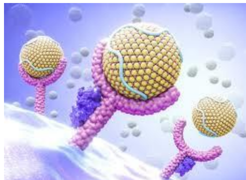




Sodium hydrogen exchanger (NHE)

- Transports of Na^+ for H^+ across the plasma membrane.
- Function: Raises pH_i and regulates cell volume.

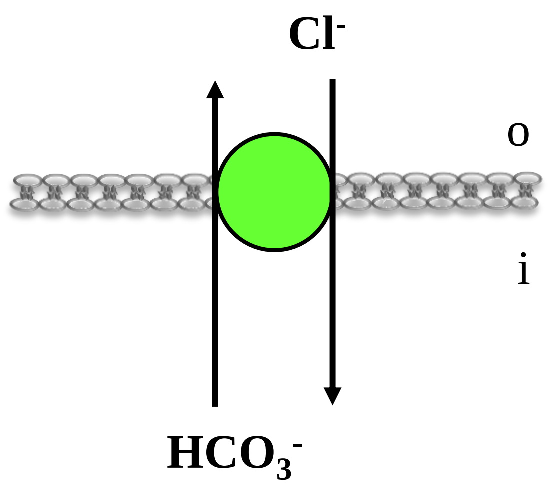


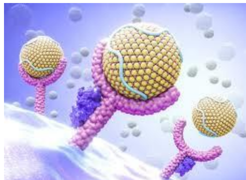


Sodium-independent anion exchanger (Cl^-/HCO_3^- exchanger)

LO1

- Exchanges of HCO_3^- for Cl^- across the plasma membrane.
- Electroneutral.
- Occurs in both directions.

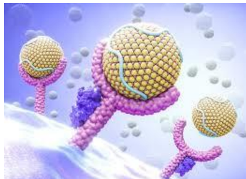




LO2&3

Control of intracellular Ca^{2+}

- Intracellular $[Ca^{2+}]$ is 50-100 nM
- Extracellular $[Ca^{2+}]$ is 2×10^6 nM
- A **20,000** fold difference in levels across the plasma membrane.
- High intracellular calcium is **toxic** to cells.
- Cells signal by small changes in intracellular $[Ca^{2+}]$.



Control of $[Ca^{2+}]_i$

LO2&3

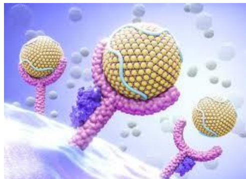
- Primary active transport
  - PMCA expels Ca^{2+} out of the cell.

    {High affinity, low capacity (removes residual Ca^{2+})}.
  - SERCA accumulates Ca^{2+} into the SR/ER.

    {High affinity, low capacity (removes residual Ca^{2+})}.
- Secondary active transport
  - Na^{+}/Ca^{2+}-exchange (NCX).

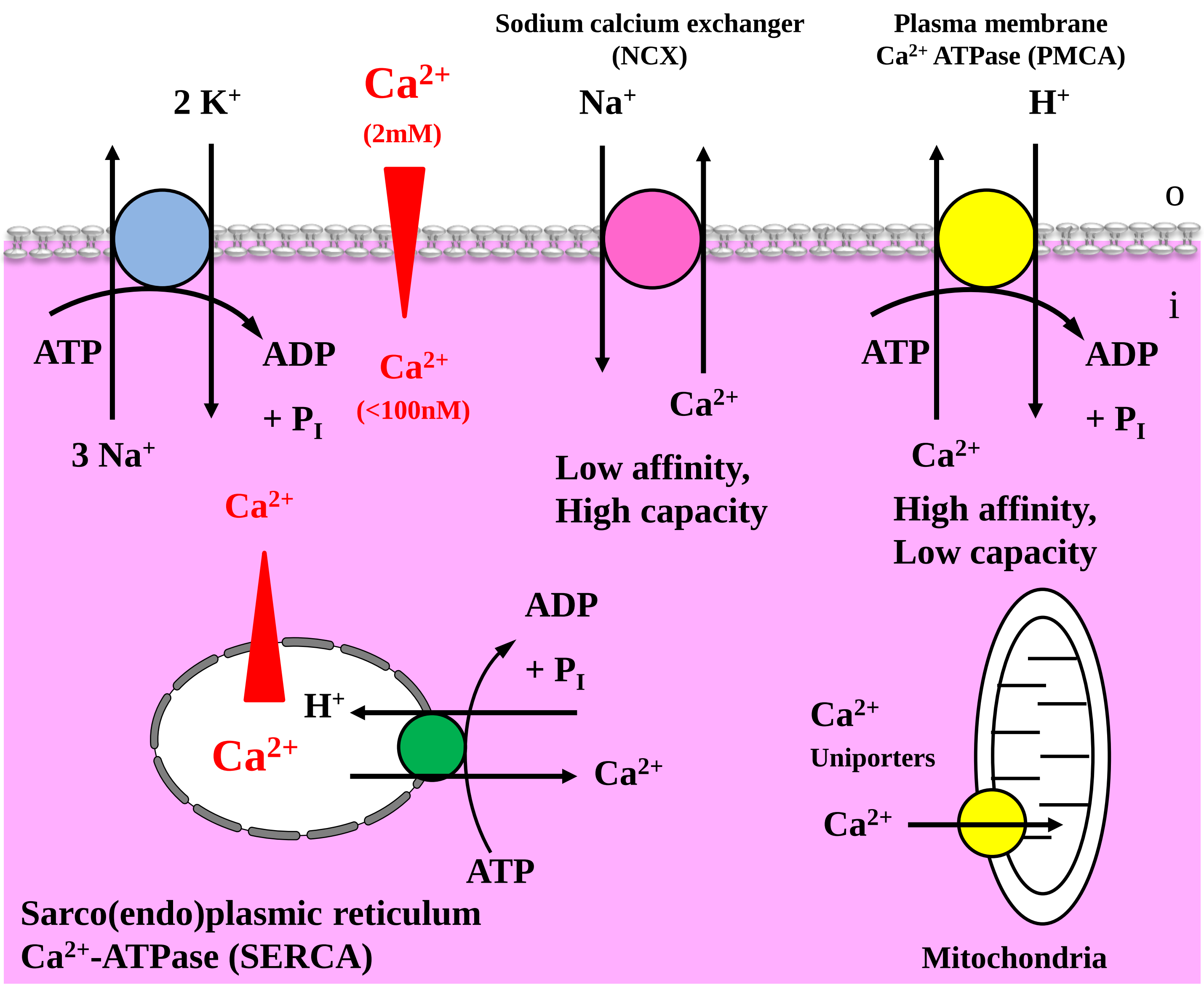
    {Low affinity, high capacity (removes most Ca^{2+})}.
  - Mitochondrial Ca^{2+} uniports.

    {Operate at high $[Ca^{2+}]_i$ to buffer potentially damaging $[Ca^{2+}]$}.



Control of resting $[Ca^{2+}]_i$

LO2&3



LO2&3

Raising $[Ca^{2+}]_i$

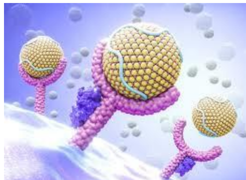
➢ Facilitated diffusion

- Receptor-operated Ca^{2+} channels (ROC).
- Voltage-operated Ca^{2+} channels (VOCC, VGCC (gated)).
- IP3-gated Ca^{2+} channels (IP3R).
- Ca^{2+} induced Ca^{2+} release (CICR) (Ryanodinesensitive Ca^{2+} channels).
- Store-operated Ca^{2+} channels (SOC).
- Mitochondrial Ca^{2+} uniports.

➢ Secondary active transport

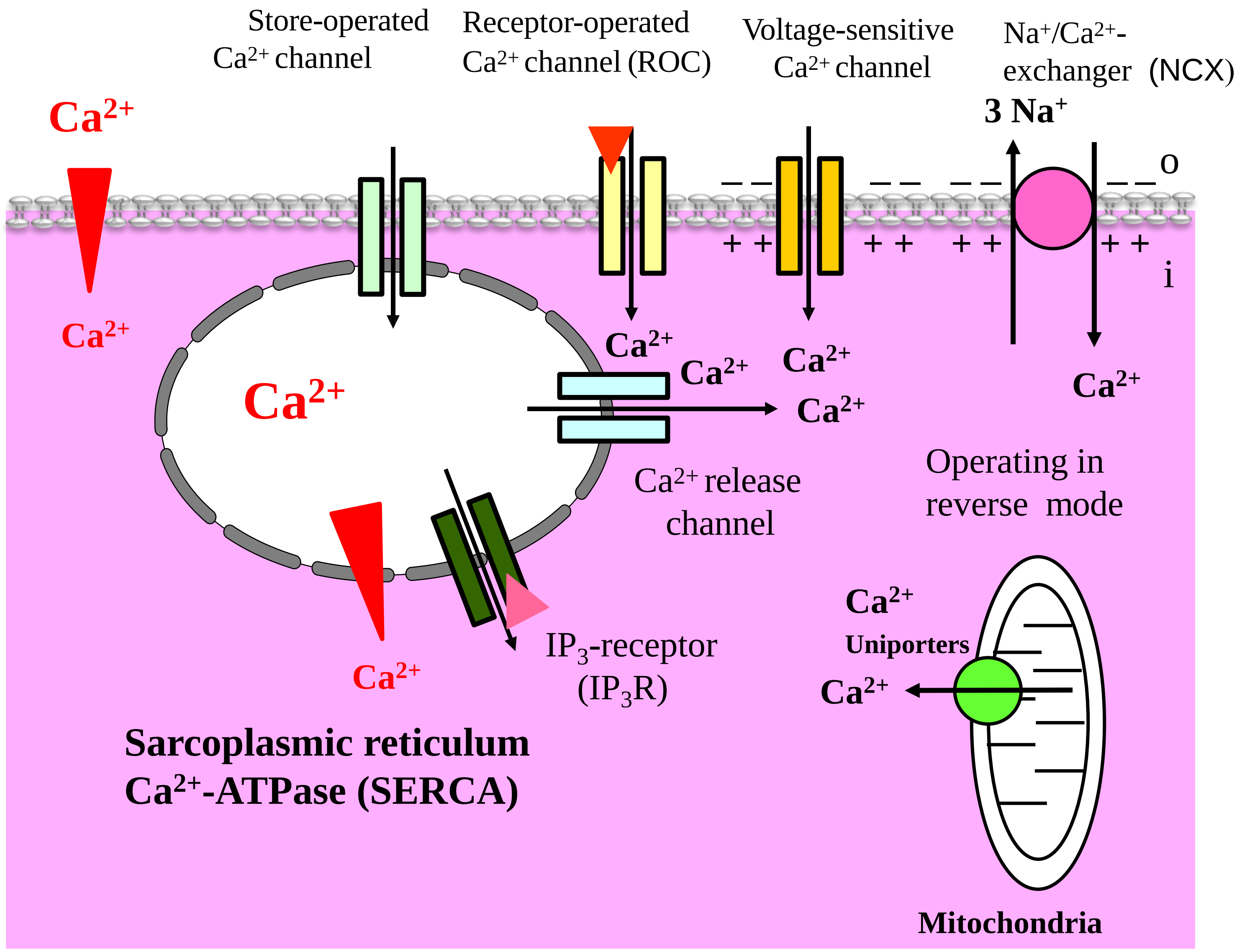
- Na^+/Ca^{2+}-exchange (NCX).

Reverse mode in depolarised cells.



Raising$[Ca^{2+}]_i$

LO2&3

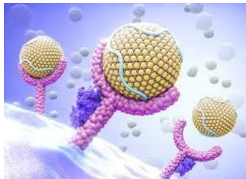


Ion transporters in cellular pH regulation

- Cellular pH is controlled by the activity of a variety of plasma membrane transporters.

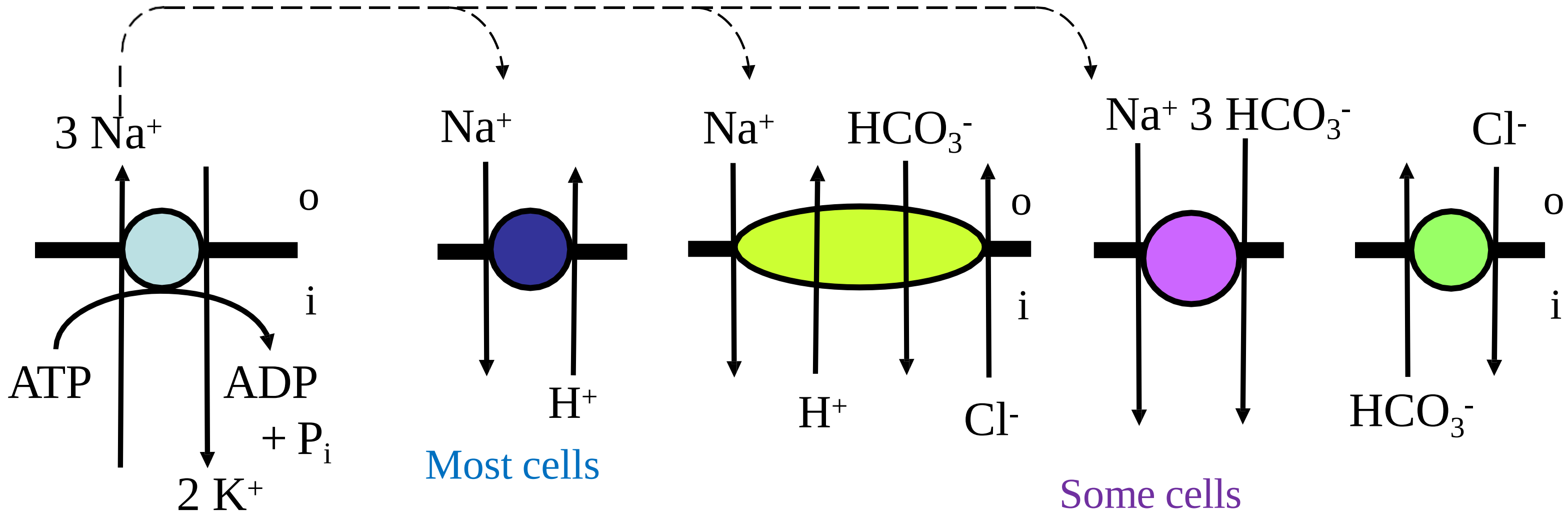
- Acidification can be opposed by expelling H^+ ions or the inward movement of HCO_3^-.

- Alkalinisation is opposed by expelling HCO_3^- via the anion exchanger.



Ion transporters in cellular pH regulation

LO2&3



All cells

Na^+/K^+-ATPase

Creates Na^+ gradient to provide energy for following transporters

Na^+/H^+-Exchange

Some cells

Na^+-Cl^--HCO-H^+ co-transport (coupled Na^+-H^+- and anion exchange)

Na^+-HCO_3^- co-transport

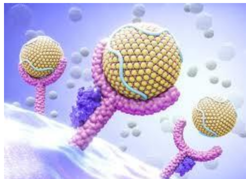
Most cells

Anion exchange (Band 3)

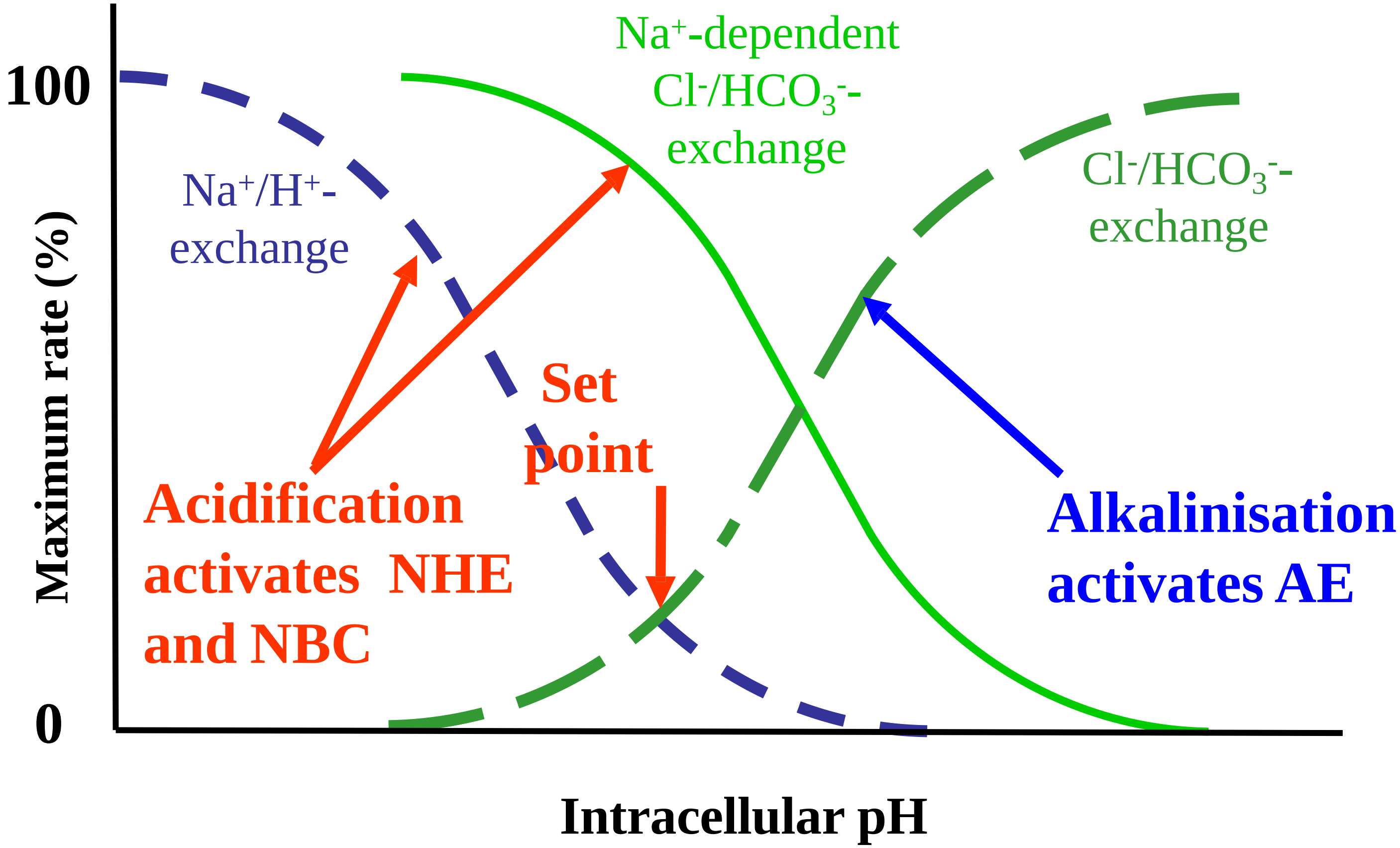
Acid extrusion

Alkali influx

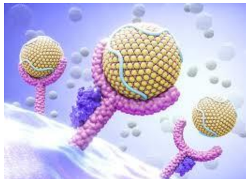
Alkali extrusion



Coordination of intracellular pH regulation



pH is held at the set point. Any drift away from this pH is corrected by the ↑ activity of either the Na^+/H^+- or Cl^-/HCO_3^- exchangers



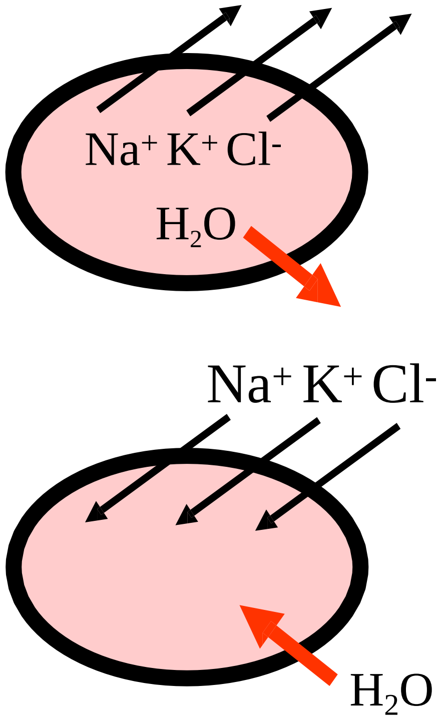
Cell volume regulation

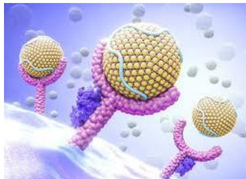
- Osmolytes (osmotically active particles (Na^+, K^+ and Cl^-) or small organic molecules) are transported to keep cell volume and prevent cell damage or death.

- Water follows.

Cell swelling – extrudes ions
Water follows

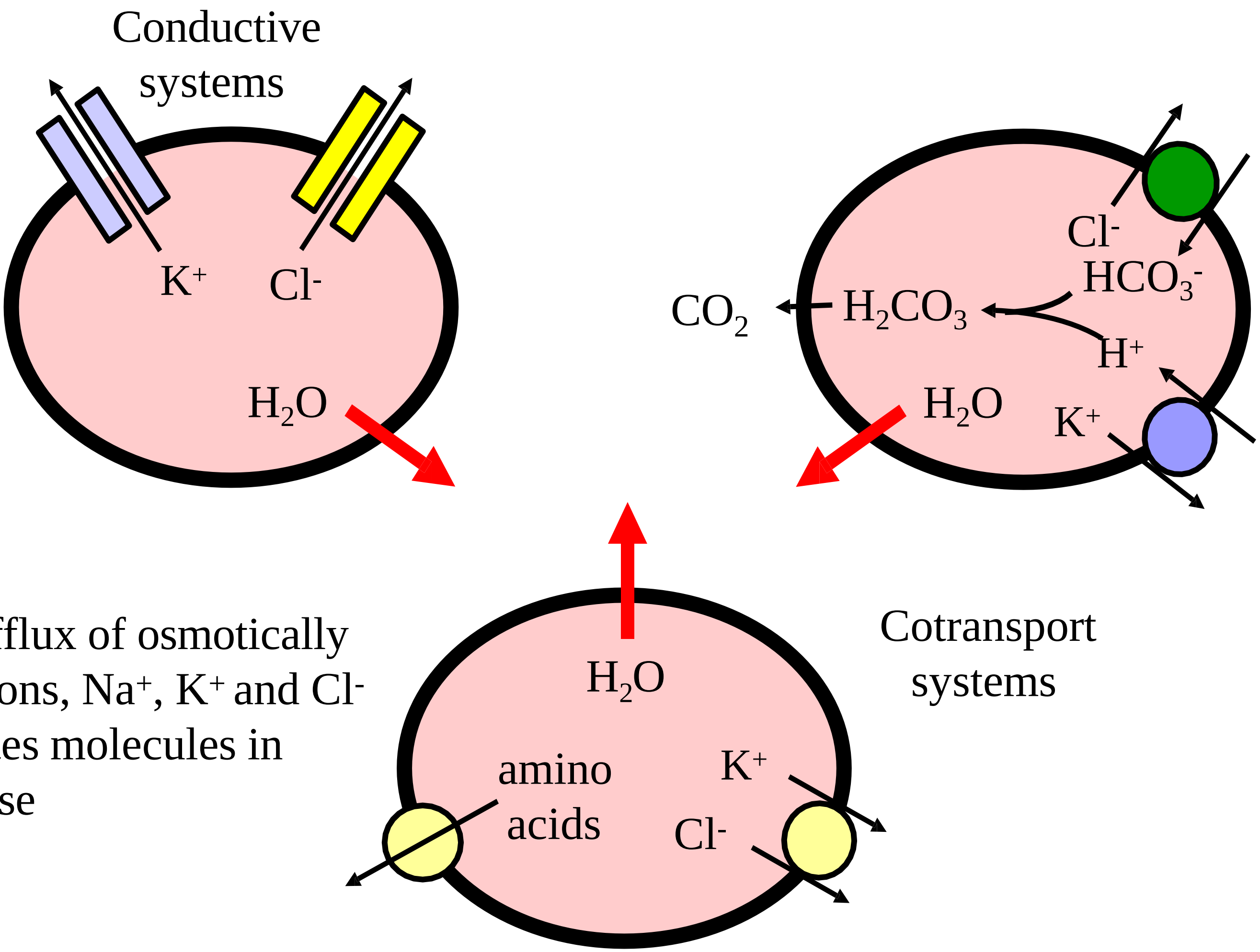
Cell shrinking – influxes ions
Water follows



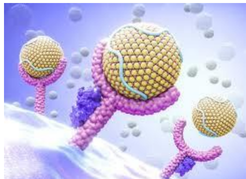


LO2&3

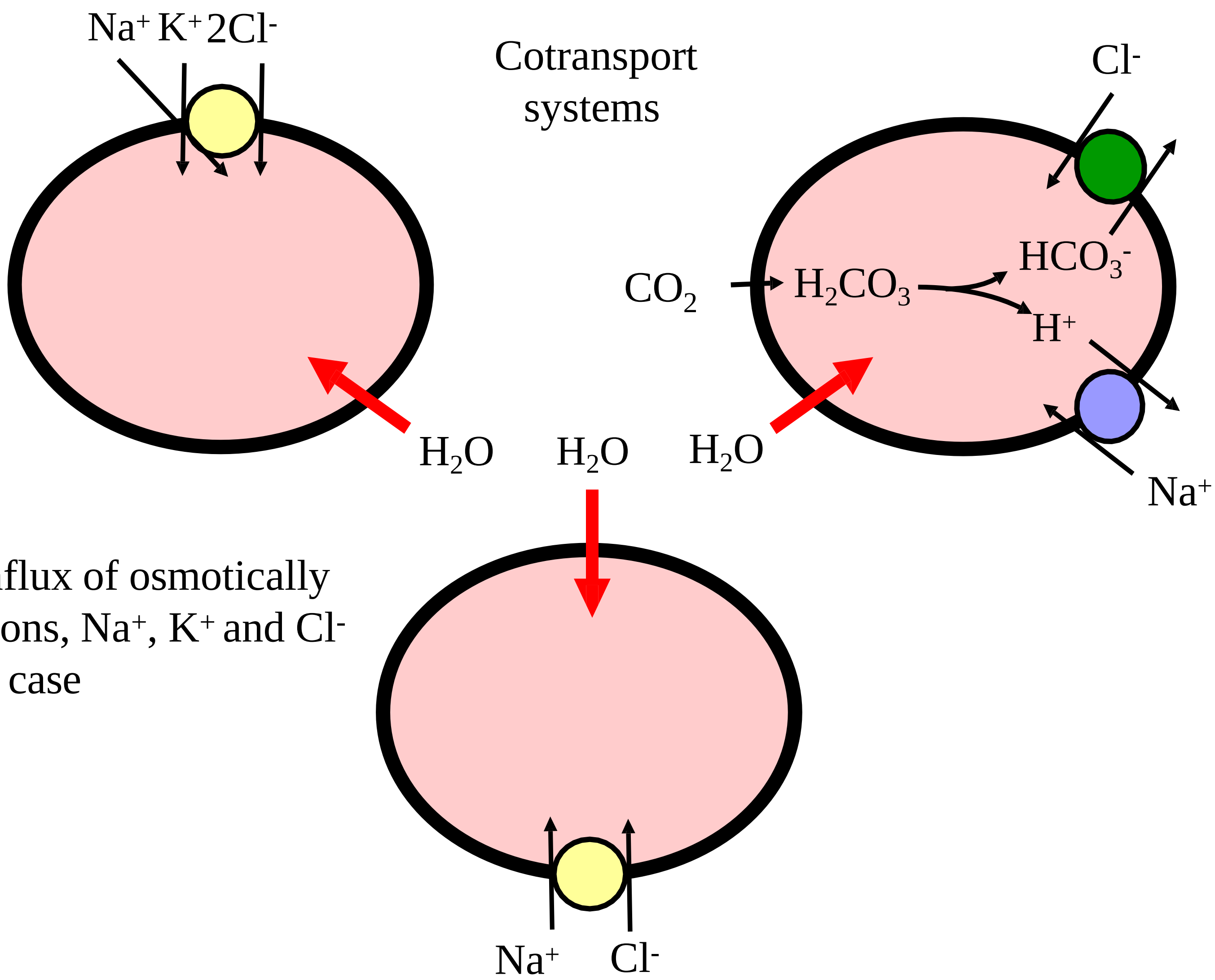
Mechanisms to resist cell swelling



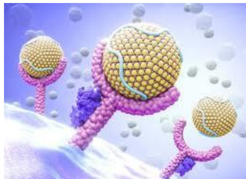
N.B. Efflux of osmotically active ions, Na^+, K^+ and Cl^- or solutes molecules in each case



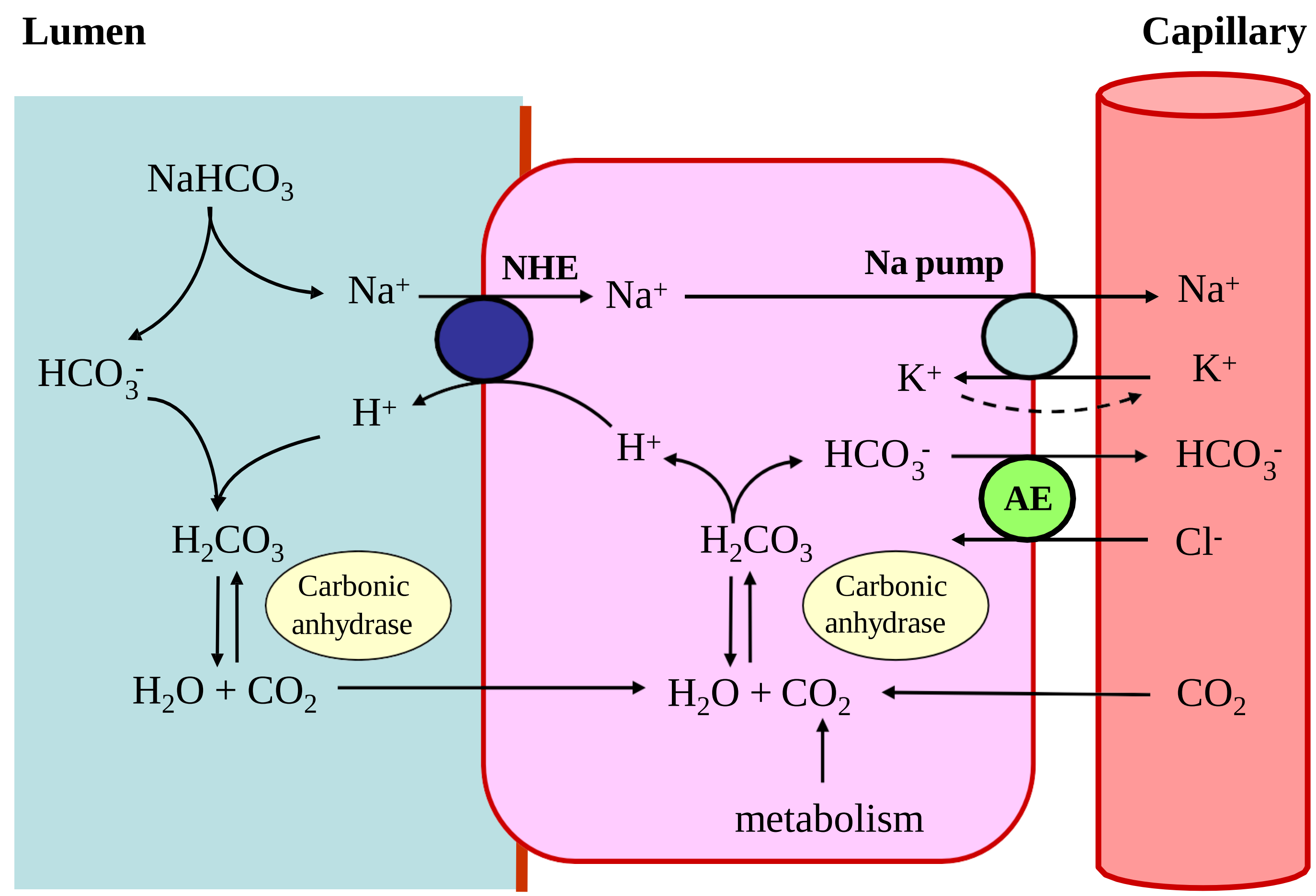
Mechanisms to resist cell shrinking



N.B. Influx of osmotically active ions, Na^+, K^+ and Cl^- in each case



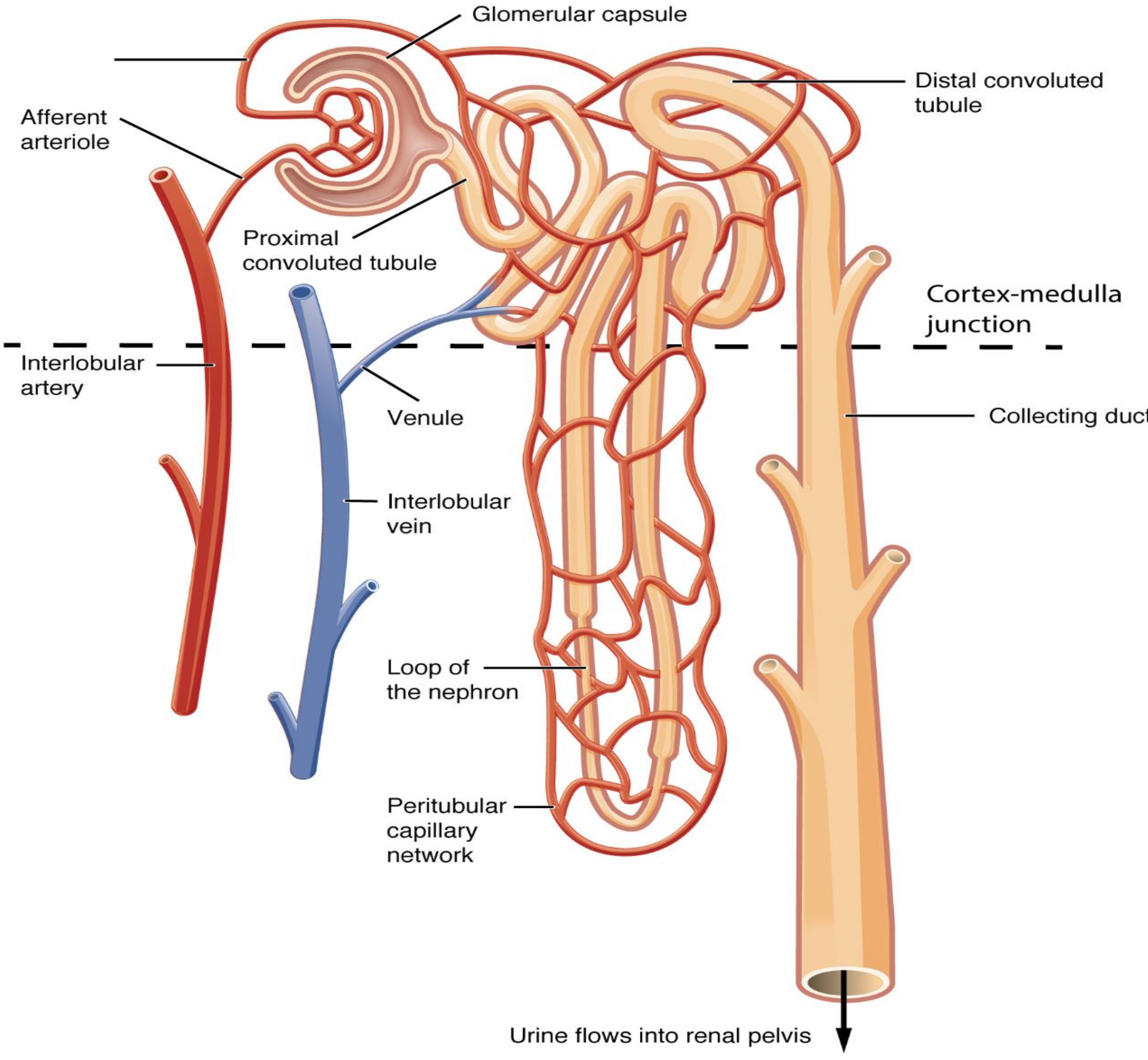
Bicarbonate reabsorption by the proximal tubule



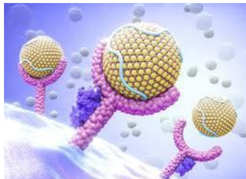
Under normal circumstances, the kidney reabsorbs all of the bicarbonate filtered into the proximal tubule. The main reason is to retain base for pH buffers.

Structure of nephron

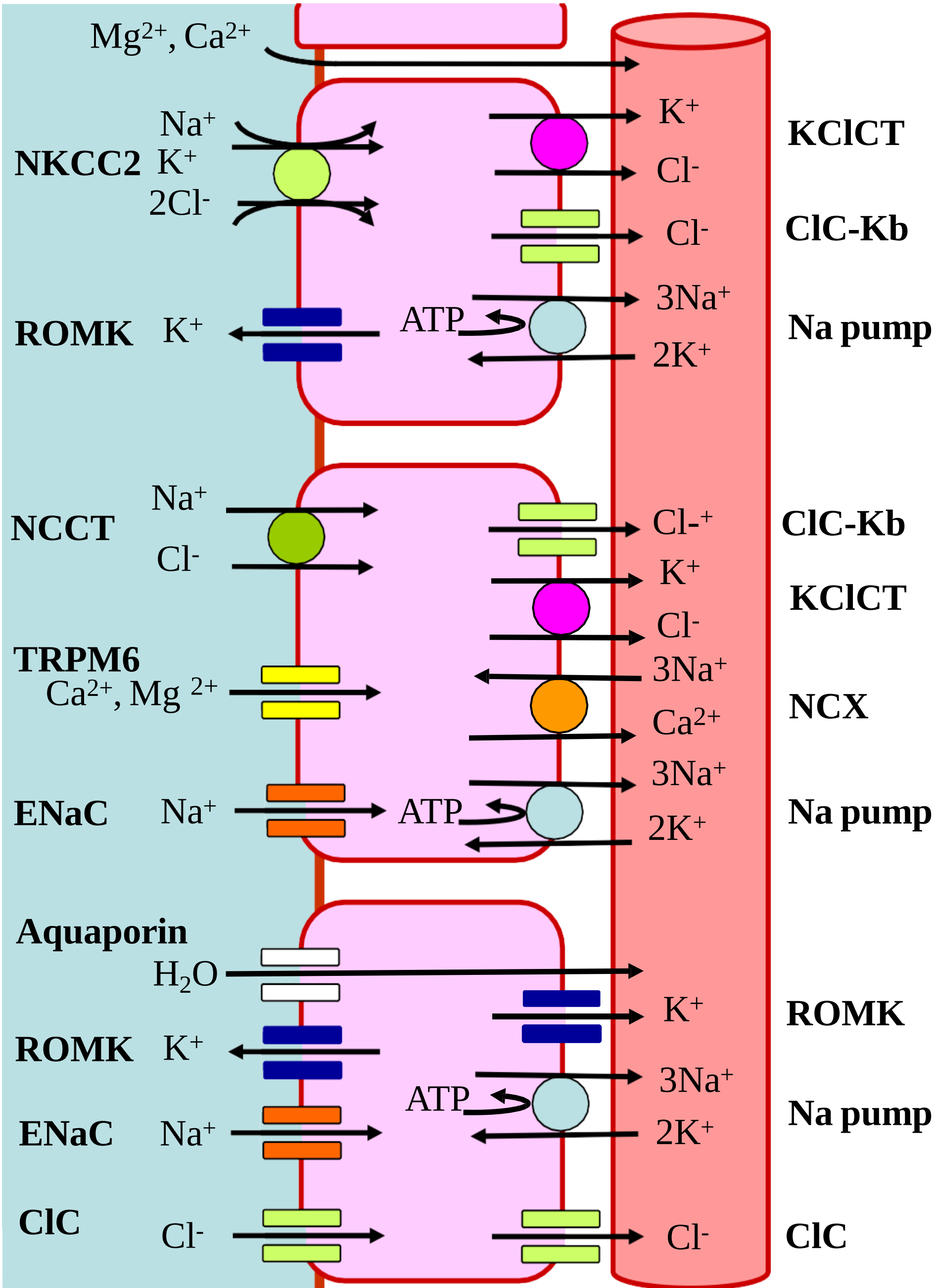
LO2&3

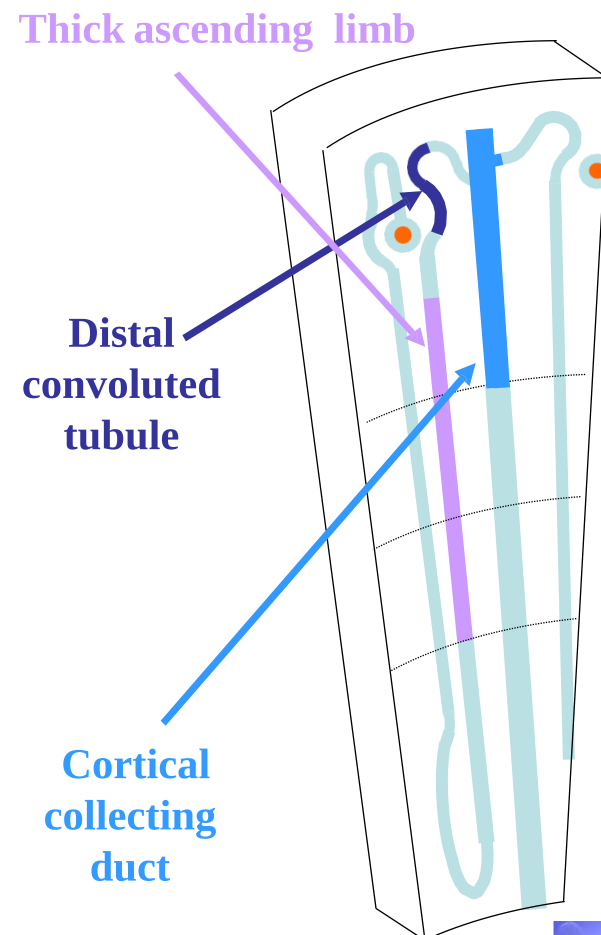


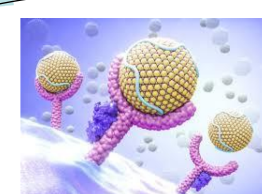
https://open.oregonstate.education/app/uploads/sites/48/2019/07/2611_Blood_Flow_in_the_Nephron_revised.png



Na^+ reuptake by the kidney

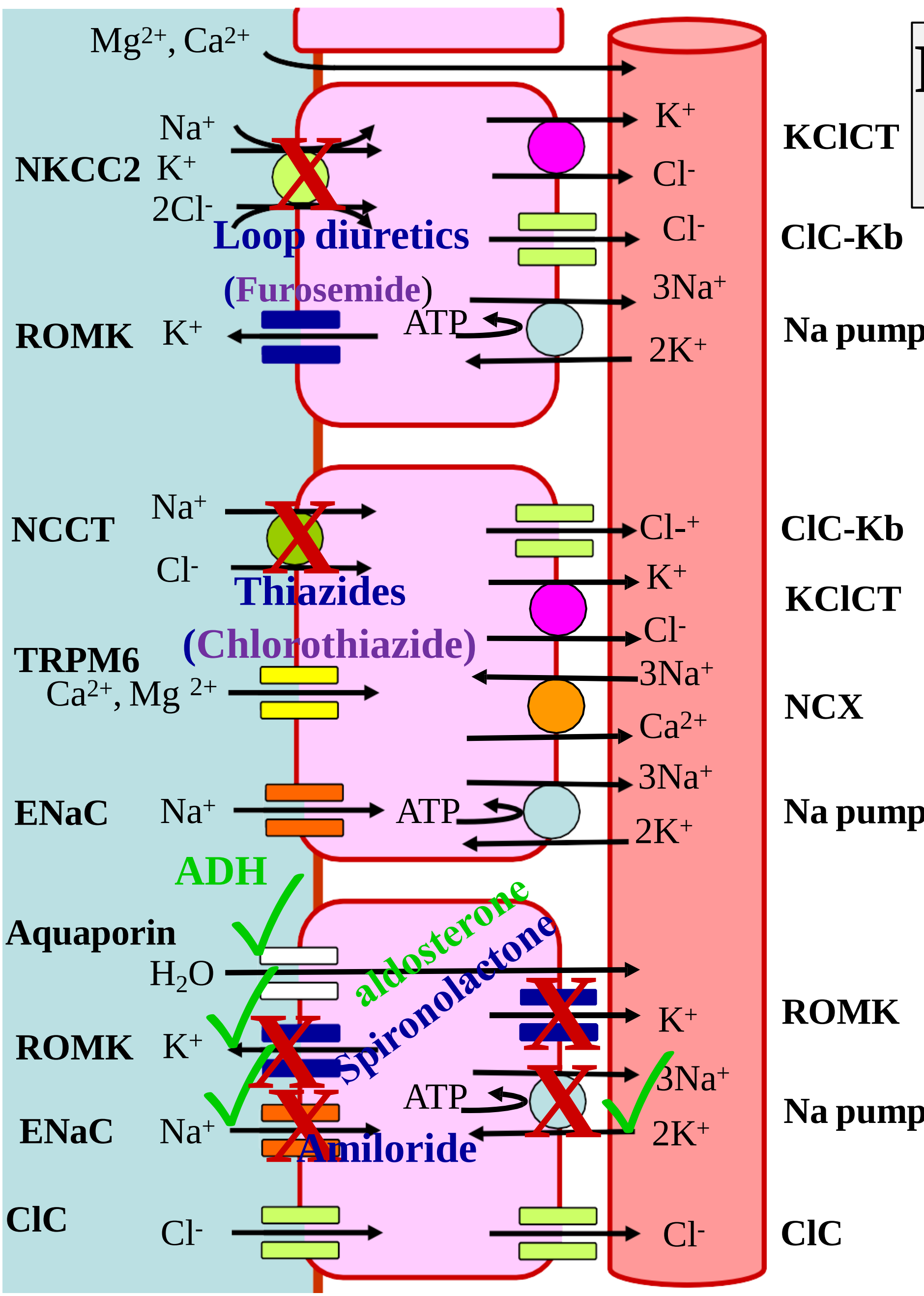


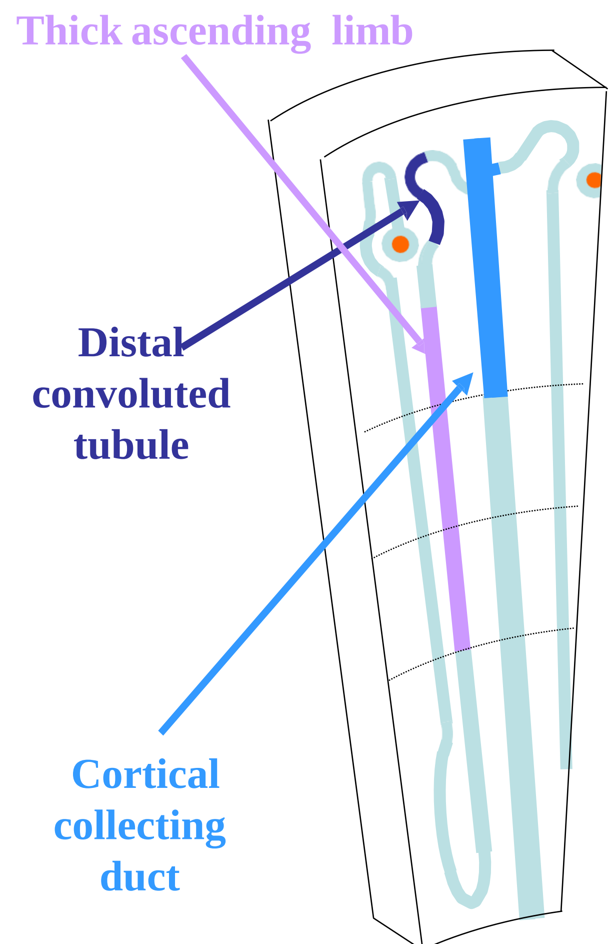


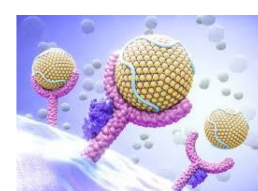


LO2&3

Renal anti-hypertensive therapy

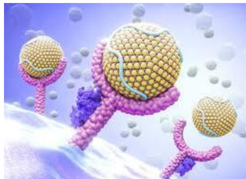






Abbreviation

- NKCC2:Sodium-Potassium-two Chloride cotransporter
- ROMK: Renal Outer Medullary Potassium channel
- NCCT: Sodium-Chloride cotransporter
- TRPM6: Transient Receptor Potential Cation Channel subfamily M6
- ENaC : Epithelial Sodium channel
- ClC: Chloride channel
- KClCT: Potassium-Chloride cotransporter
- ClC-kb: Chloride channel type kb



Thank you