BME 5742 Biosystems Modeling and Control

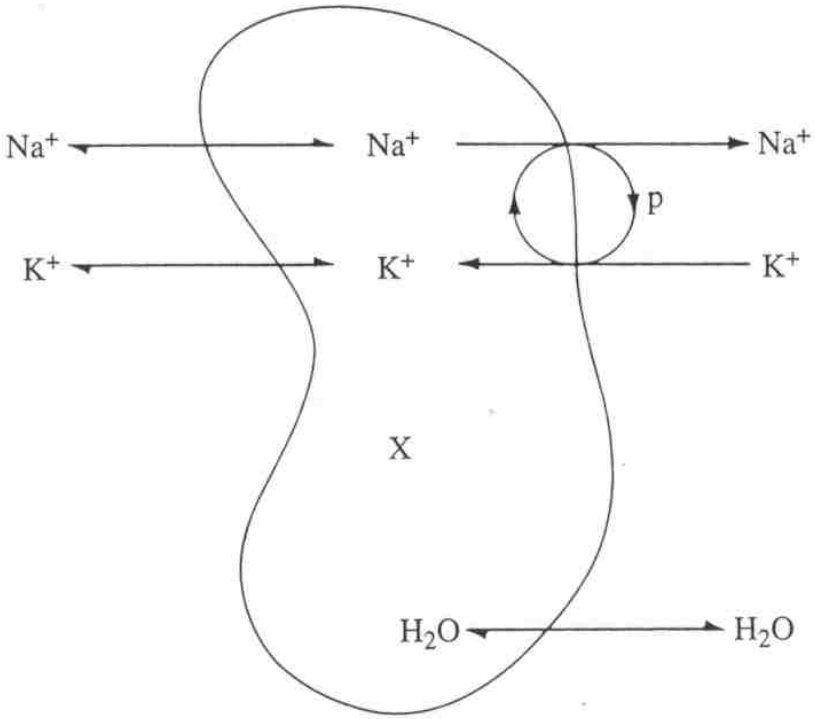
Lecture 31

The Sodium-Potassium Pump and Simplified Cell Volume Control

References

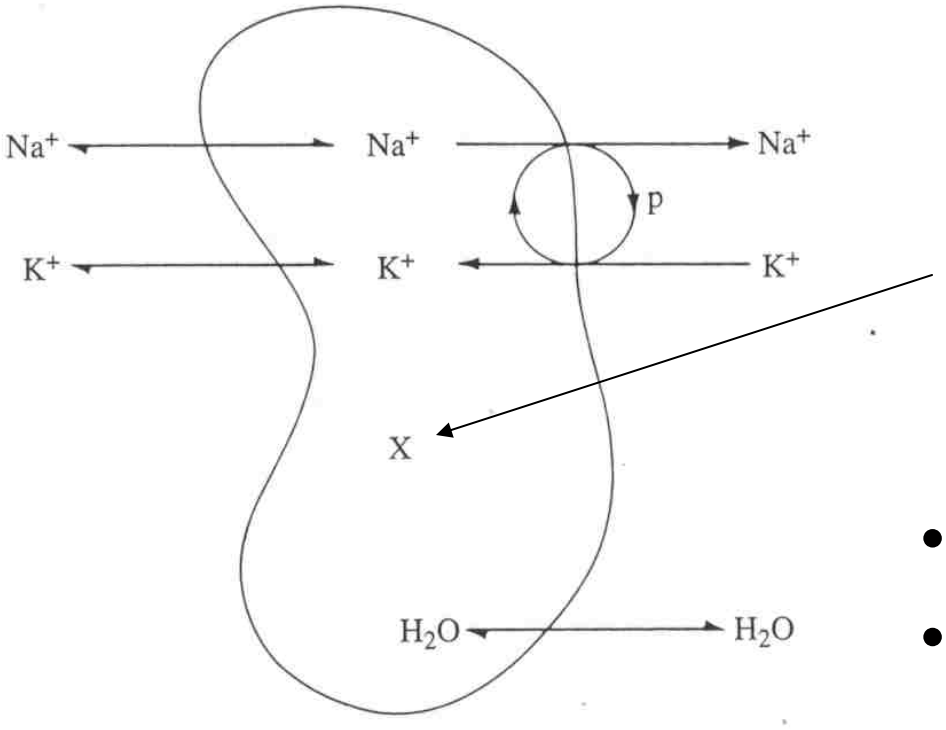
- Hoppensteadt and Peskin Chapter 3.
- Geoffrey M. Cooper “The Cell – A Molecular Approach”, ASM Press 1997. (regarding the operation of the Na^+-K^+ pump)
- Keener and Sneyd “Mathematical Physiology”, Springer 1998.

Simple Cell Volume Control Model



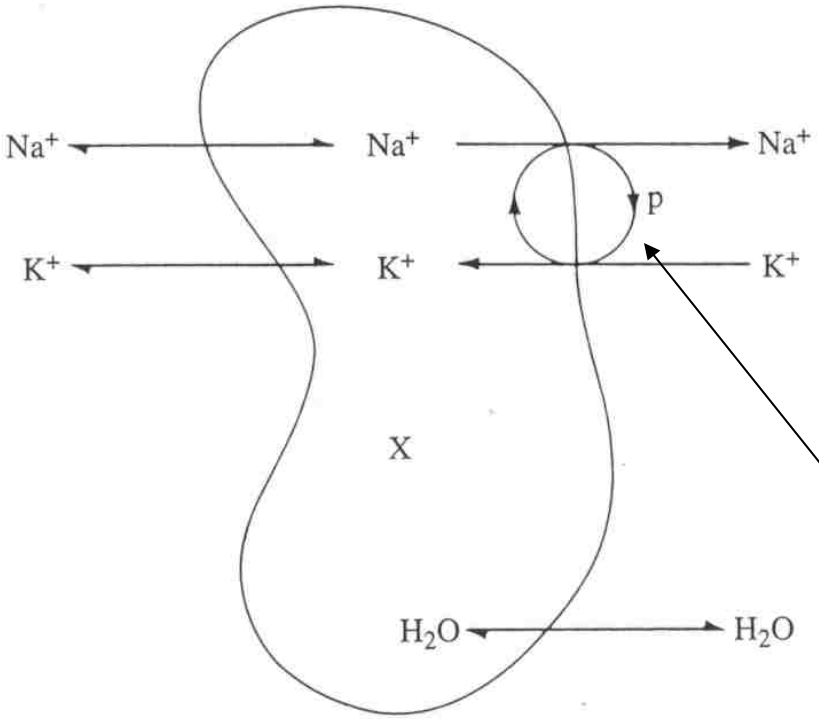
- <u>Goals</u>: Achieve cellular osmotic balance, and cell volume control.
- Model is simplified because we disregard electrical effects – this will be added soon.

Large Molecules in the Cell



- X represents the number of all intracellular large molecules, that cannot permeate through the cell membrane.
- V is the cell volume.
- X / V is the large molecules concentration.

Other Cell substances included in the model

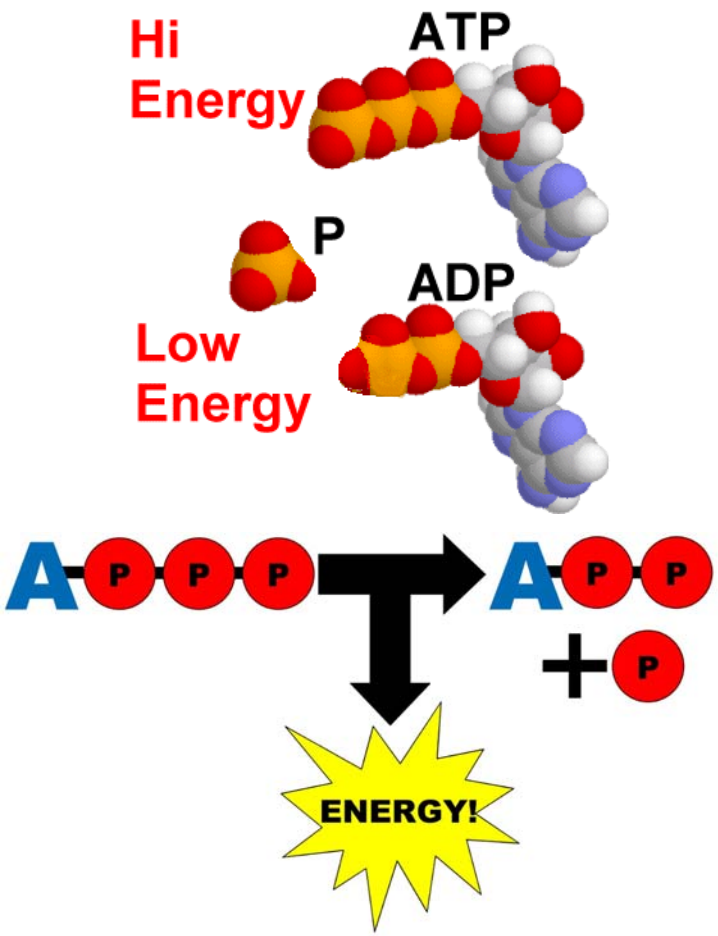


- Cell contains Na^+ and K^+ ions. These ions can diffuse back and forth through the cell membrane.
- Membrane is also permeable to water.
- Cell membrane has “pumps” that can pump internal Na^+ ions out in exchange for external K^+ ions.

Sodium-Potassium Pump

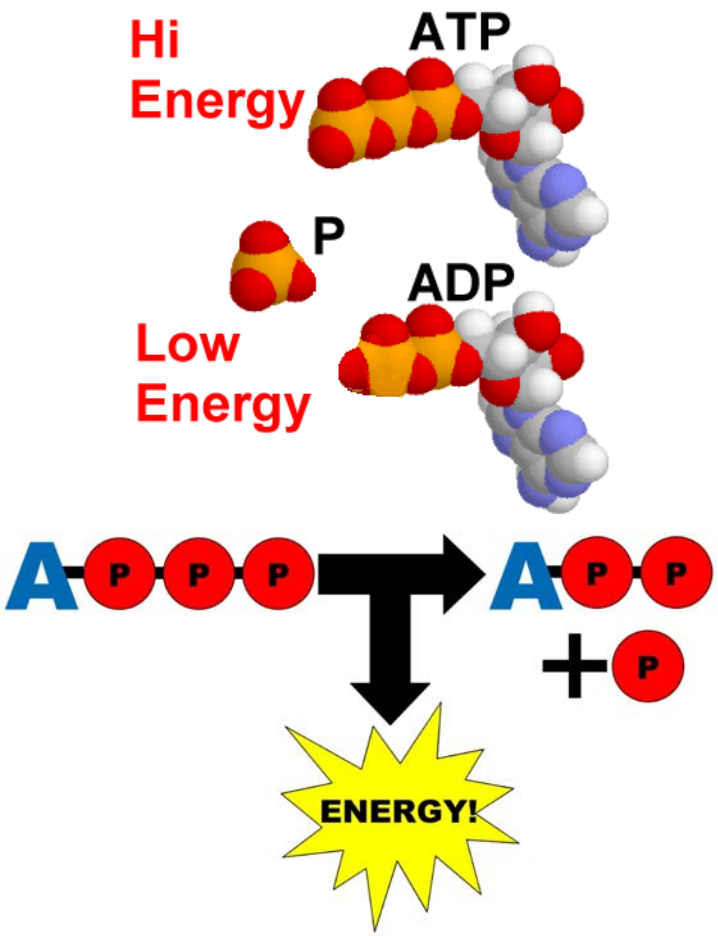
- The usual facilitated diffusion of molecules is in the energetically “downhill” direction.
- Sometimes there is a need to transport molecules against their concentration gradient. This is done by a “pump”.
- Energy source for the pump is the hydrolysis process of ATP molecules.
- The next slides (taken from Cooper’s book) illustrate how the above pump works.

ATP (Adenosine triphosphate) and ADP



- Present in the cell are ADP (adenosine diphosphate) and phosphate molecules. An energy needs to be invested to loosely bond a third phosphate to ADP, creating ATP.
- When a molecule of glucose is broken down into CO_2 and water with a release of energy, the cell uses some of this energy to synthesize ATP

ATP (Adenosine triphosphate) and ADP

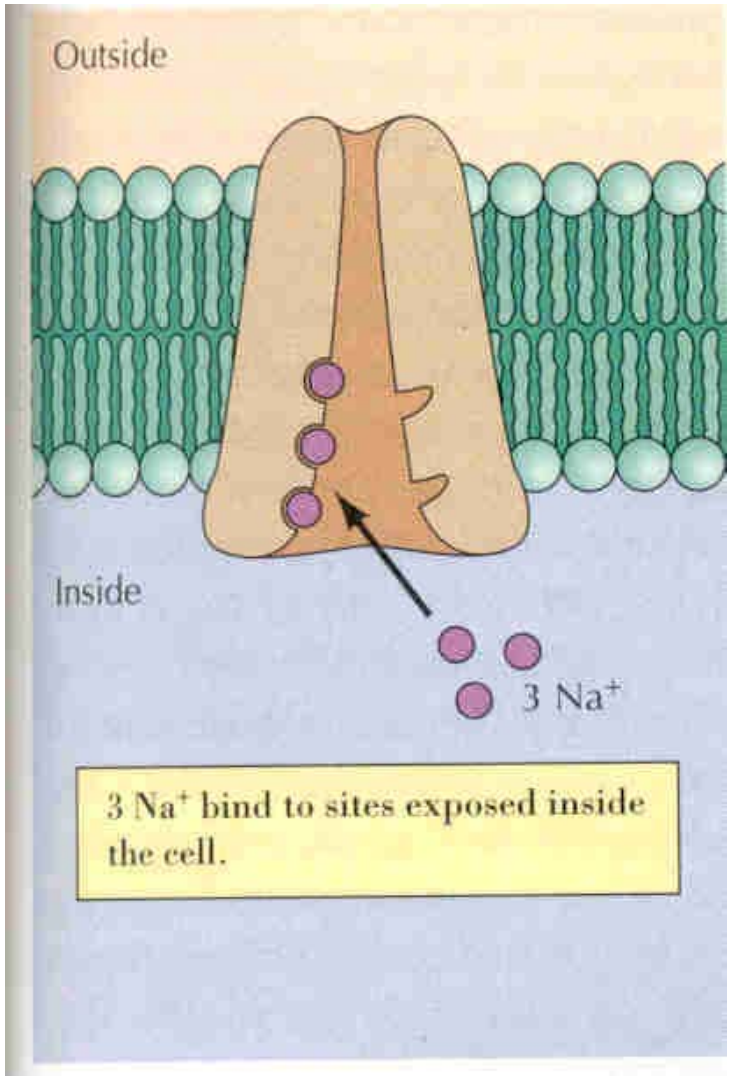


- ATP is a product of cell respiration and it contains biologically useful energy.

ATP (Adenosine triphosphate) as a Source of Energy for the Cell

- When the bond of this third phosphate is again broken and energy is released, this energy can be the source for some important cell processes.
- All cells have enzymes that can remove the third phosphate group from ATP to release its energy, forming ADP and phosphate.
- As cell respiration continues, ATP is re-synthesized. It's a continuous process.

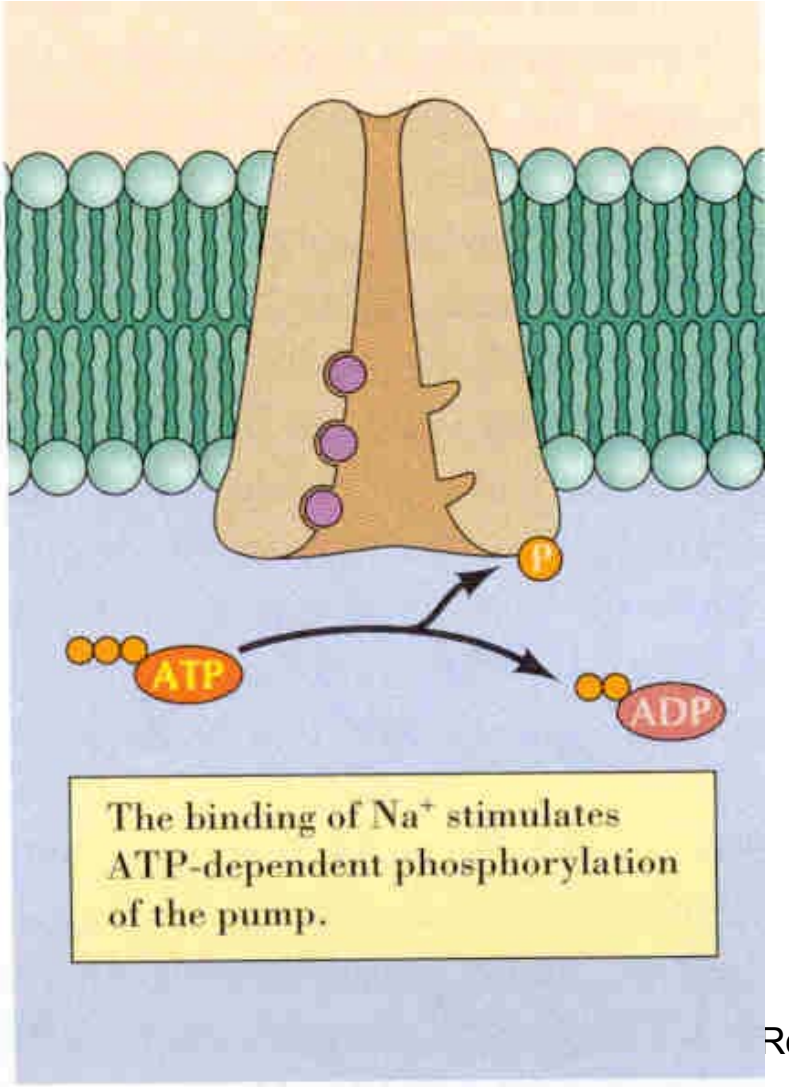
Sodium-Potassium Pump Operation - 1



<u>Step 1</u>

- (Concentration of Na^+ outside the cell is about 10 times larger than that inside the cell.) Yet:
- Inside Na^+ ions bind to 3 high-affinity sites exposed inside the cell.

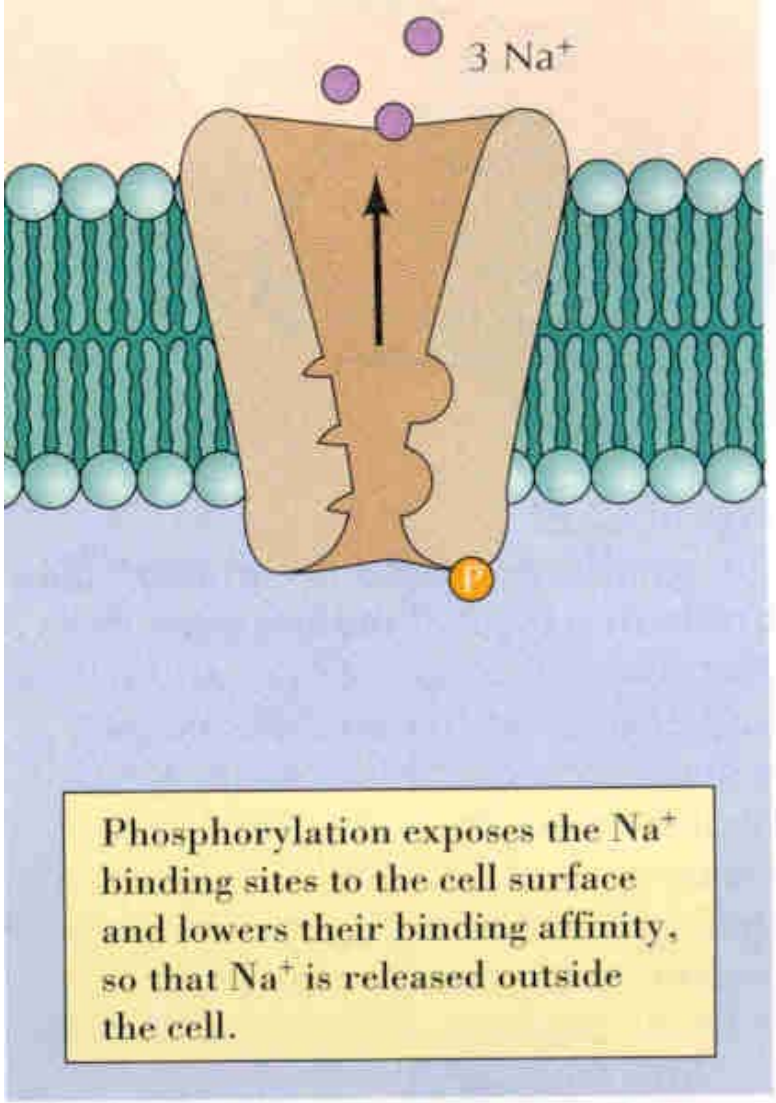
Sodium-Potassium Pump Operation - 2



Step 2

- The binding of Na^+ stimulates hydrolysis of ATP, and ATP-dependent phosphorylation of the pump.
- One atom of P binds (and creates conformational changes in the pump.)

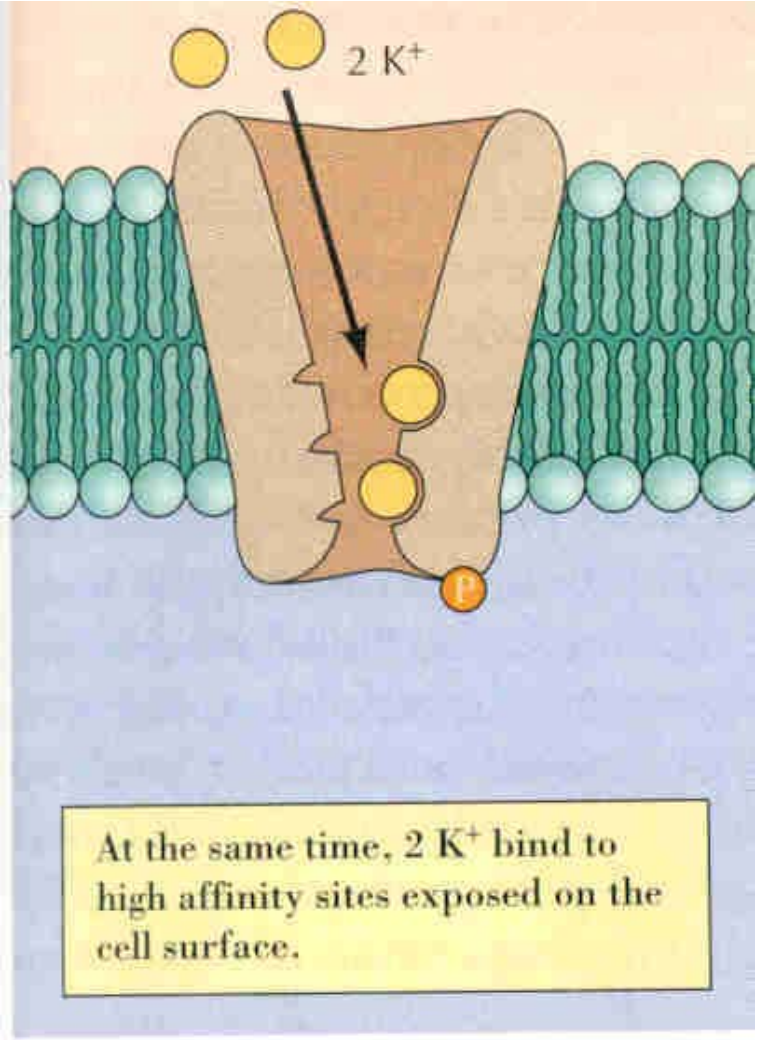
Sodium-Potassium Pump Operation - 3



<u>Step 3</u>

- The binding of P to the pump wall induces conformational change that exposes the Na^+ binding sites to the outside of the cell.
- It also reduces the affinity of these sites → 3 Na^+ ions released to the ECF.

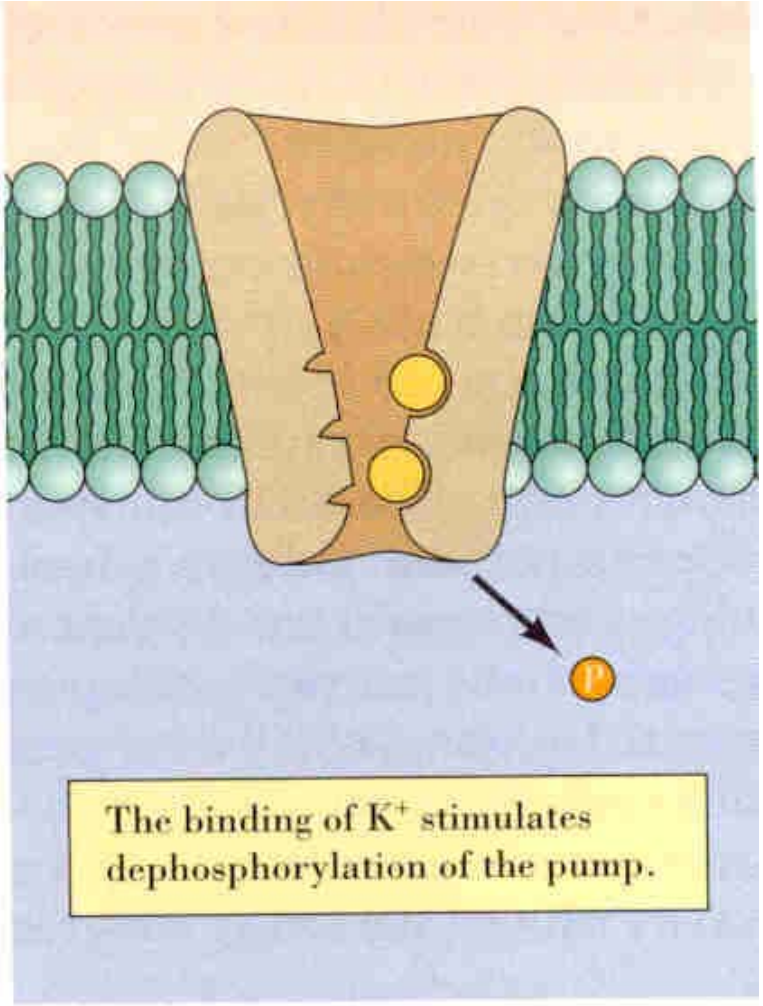
Sodium-Potassium Pump Operation - 4



Step 4

- (ICF concentration of K^+ is much higher than ECF's). Yet:
- At the same time that 3 Na^+ ions leave the cell, 2 K^+ outside ions sneak into two high-affinity sites that become exposed to the outside.

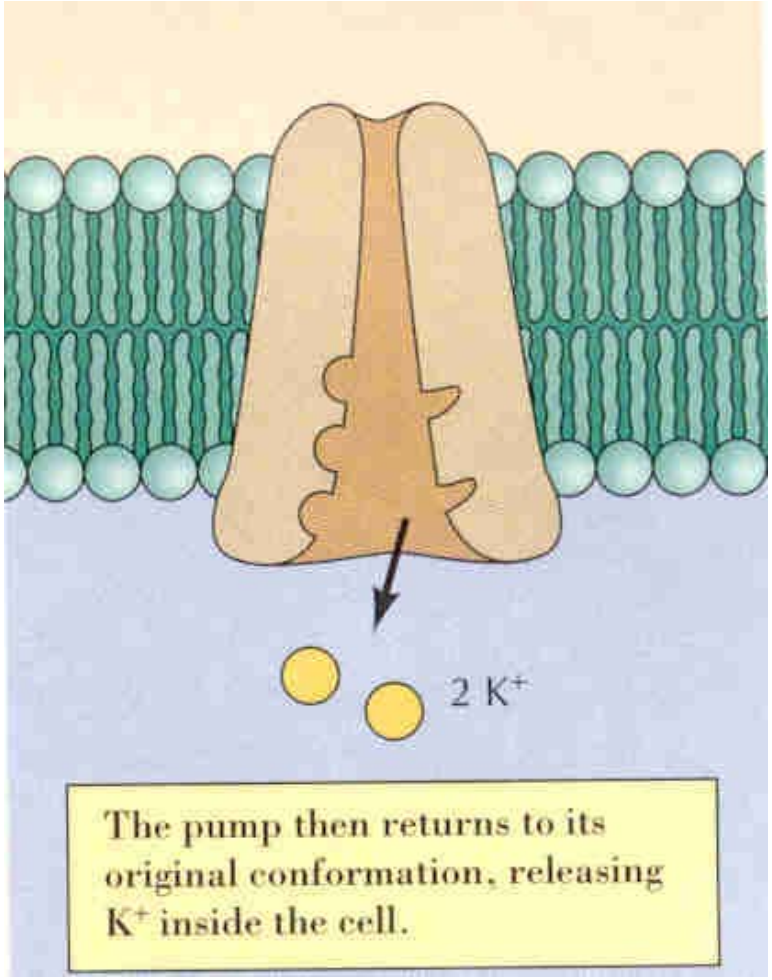
Sodium-Potassium Pump Operation - 5



<u>Step 5</u>

- The binding of K^+ to the pump's sites stimulates a dephosphorylation of the pump.
- P atom leaves the pump (this restores the original pump conformation)

Sodium-Potassium Pump Operation - 6



Step 6

- The conformational change due to the leaving of P, reduces the affinity of the K^+ binding sites.
- 2 K^+ ions are therefore released into the ICF.
- Na^+ binding sites become exposed again.

Pump Operation Summary

- One cycle of a single cell's pump moves 3 Na^+ ions to the ECF, and 2 K^+ ions to the ICF, at the expense of one ATP molecule.
- Na^+-K^+ pumps consume nearly 25% of the ATP used by many cells.
- Pumping rate depends on the amount of ATP molecules in the cell, and on the ECF and ICF concentrations of Na^+ and K^+.

Fundamental Property of Human and Animal Cells

- The pressure inside the cell must equal the pressure outside the cell.
- Cell membranes cannot withstand any hydrostatic pressure difference.
- If ICF concentrations of various ions and larger molecules becomes too large, osmotic forces cause entry of water into the cell, causing it to swell and burst.

Net Ions Outwards Flux -1

$$f_{Na} = \alpha_{Na}([Na^+]_i - [Na^+]_o) + p$$

$$f_K = \alpha_K([K^+]_i - [K^+]_o) - p$$

$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + \frac{X}{V} - [Na^+]_o - [K^+]_o)$$

- The flux f (in ions per unit time) is positive in the outwards direction.
- Pump rate is p. As an approximation we assume that one Na^+ is exchanged for one K^+. Actually the ratio is 3:2, as we have seen.

Net Ions Outwards Flux -2

$$f_{Na} = \alpha_{Na}([Na^+]_i - [Na^+]_o) + p$$

$$f_K = \alpha_K([K^+]_i - [K^+]_o) - p$$

$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + \frac{X}{V} - [Na^+]_o - [K^+]_o)$$

- The coefficients α_{Na} and α_K are the passive permeabilities of the cell to Na and K ions.
- R_{H2O} is the cell membrane's resistance to flow of water.
- The subscripts "I" and "o" designate inside and outside of the cell.

Net Ions Outwards Flux -3

$$f_{Na} = \alpha_{Na}([Na^+]_i - [Na^+]_o) + p$$

$$f_K = \alpha_K([K^+]_i - [K^+]_o) - p$$

$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + \frac{X}{V} - [Na^+]_o - [K^+]_o)$$

- The third equation arises from the assumption that $P_i = P_o$.
- Equation takes into account all osmotic pressures of the various molecule types.

Net Ions Outwards Flux -1 (no approximation)

$$f_{Na} = \alpha_{Na}([Na^+]_i - [Na^+]_o) + 3p$$

$$f_K = \alpha_K([K^+]_i - [K^+]_o) - 2p$$

$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + \frac{X}{V} - [Na^+]_o - [K^+]_o)$$

- The flux f (in ions per unit time) is positive in the outwards direction.

For cell at steady-state net flux is zero:

$$[Na^+]_i - [Na^+]_o = -\frac{p}{\alpha_{Na}}$$

$$[K^+]_i - [K^+]_o = \frac{p}{\alpha_K}$$

$$[Na^+]_i + [K^+]_i + \frac{X}{V} = [Na^+]_o + [K^+]_o)$$

- Total concentration of solutes must be equal inside and outside the cell ←→ Osmotic balance.
- Pumping rate creates the needed ion concentration differences.

What would happen if [X]=0?

$$[Na^+]_i - [Na^+]_o = -\frac{p}{\alpha_{Na}}$$

$$[K^+]_i - [K^+]_o = \frac{p}{\alpha_K}$$

$$[Na^+]_i + [K^+]_i = [Na^+]_o + [K^+]_o)$$

- Total concentration of solutes must be equal inside and outside the cell ←→ Osmotic balance.
- Pumping rate creates the needed ion concentration differences.

For cell at steady-state net flux is zero: (no approximation)

$$[Na^+]_i - [Na^+]_o = -\frac{3p}{\alpha_{Na}}$$

$$[K^+]_i - [K^+]_o = \frac{2p}{\alpha_K}$$

$$[Na^+]_i + [K^+]_i + \frac{X}{V} = [Na^+]_o + [K^+]_o)$$

- Total concentration of solutes must be equal inside and outside the cell.
- Pumping rate creates ion concentration differences

Simplified Volume Control Mechanism

$$[Na^+]_i - [Na^+]_o = -\frac{p}{\alpha_{Na}} \qquad [K^+]_i - [K^+]_o = \frac{p}{\alpha_K}$$

$$\Rightarrow [Na^+]_i + [K^+]_i + \frac{X}{V} = [Na^+]_o + [K^+]_o)$$

$$\Rightarrow \frac{X}{V} = p(\frac{1}{\alpha_{Na}} - \frac{1}{\alpha_K}) = p\frac{\alpha_K - \alpha_{Na}}{\alpha_K \alpha_{Na}}$$

Substitution of the first two equations into the third one, reveals the relationship between pump action and volume of the cell.

Cell Volume Control Interpretation - 1

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- For V>0 it is necessary that $\alpha_K > \alpha_{Na}$.
- If for some reason $\alpha_K < \alpha_{Na}$ then there is no steady-state: V increases until cell bursts.

Cell Volume Control Interpretation - 2

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- Cell membrane has to be more permeable to K^+ than to Na^+.
- Recall that pump pushes Na^+ out and K^+ in.

Cell Volume Control Interpretation - 3

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- Diffusion through the membrane partially offsets the work of the pump.
- The net effect of the pump is to reduce ions concentrations in the cell.

Cell Volume Control Interpretation - 4

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- Pump action makes it possible to offset the osmotic effect of the large molecules that are trapped inside the cell.
- Without a pump the cell would not be able to reach osmotic balance and steady state.

Cell Volume Control Interpretation - 5

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- Note that cell volume V depends inversely on the pump rate p.
- As p→0, V increases: “Dead cells swell”.

Cell Volume Control Interpretation - 6

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{\alpha_K - \alpha_{Na}}$$

- Note that V is proportional to X.
- Cell volume is automatically adjusted to the number of proteins and other macromolecules trapped within the cell.
- As cell produces more molecules, its volume increases proportionately.

Simplified Volume Control Mechanism (no approximation)

$$[Na^+]_i - [Na^+]_o = -\frac{3p}{\alpha_{Na}} \qquad [K^+]_i - [K^+]_o = \frac{2p}{\alpha_K}$$

$$\Rightarrow [Na^+]_i + [K^+]_i + \frac{X}{V} = [Na^+]_o + [K^+]_o)$$

$$\Rightarrow \frac{X}{V} = \frac{3p}{\alpha_{Na}} - \frac{2p}{\alpha_K} = p\frac{3\alpha_K - 2\alpha_{Na}}{\alpha_K \alpha_{Na}}$$

Substitution of the first two equations into the third one, reveals the relationship between pump action and volume of the cell.

Cell Volume Control Interpretation – no approximation

$$V = \frac{X}{p} \frac{\alpha_K \alpha_{Na}}{3\alpha_K - 2\alpha_{Na}}$$

- For V>0 it is necessary that $3\alpha_K > 2\alpha_{Na}$.
- If for some reason $3\alpha_K < 2\alpha_{Na}$ then there is no steady-state: V increases until cell bursts.