Bio Inorganic Chemistry

Metal Complexes in Medicine:

Cisplatin: Anticancer Drug

Chemotherapy is the main weapons in the fight against cancer. The antitumor activity of simple square planar Pt(II) complex, cis-diammine dichloroplatinum (II) cisplatin $[Pt(NH_3)_2Cl_2]$ is known to inhibit otherwise rapid division of tumor cell.

The exact action of this complex is not known. But the studies indicate that Pt- binds with N_7 of two intrastand adjacent guanine bases of DNA. This binding changes the replication or cell division.
The binding of cisplatin to DNA seriously interferes with the ability of Guanine bases to undergo Watson-Crick base pairing

$$cis-[Pt(NH_3)_2Cl_2] + H_2O \rightleftharpoons cis-[Pt(NH_3)_2Cl(H_2O)]^+ + Cl^-$$

$$\downarrow DNA$$

$$cis-[Pt(NH_3)_2Cl]-DNA$$

$$\rightleftharpoons +H_2O \quad -Cl^-$$

$$[cis-Pt(NH_3)_2(H_2O)]-DNA \xrightarrow{DNA} cis-[Pt(NH_3)_2]=DNA$$

→ Administered by IV (aq. saline sol^{n})

→ ½ of Pt binds to serum proteins and is excreted

→ It remains as cis - $Pt(NH_3)_2Cl_2$, % of high Cl^- conc in serum

→ As a neutral molecule cisplatin diffuses passively across cell membrane into cytoplasm, here Cl^- is at lower conc.

→ Due to hydrolysis, cis platin produces cis $[Pt(NH_3)_2(OH_2)Cl]^+$ a cationic specie that diffuses to DNA.
DNA itself being anionic, it forms cytotoxic lesions

→ Both cis platin and trans platin alter the double helical structure of DNA and its replication. But trans-isomer (is resorbed more rapidly than cis platin) concentration of DNA coordinated trans complex begin to decrease after 6 hrs. where as cis isomer remains accumulated in cell nucleus.
This indicates that the changes caused by trans isomer are sensed differently by the endogenous repair mechanism than that caused by cis form.

"Basically as cisplatin binds with DNA, a structure specific recognition protein (SSRP) recognises the bending of DNA containing cis-platin and binds with DNA". This protein binds specifically with cis and not with trans. Hence making trans inactivity.

→ cis platin most effective against testicular cancer.
→ It has negative side effects in kidney and neuro-toxic

Transport Across the membrane :- ION PUMP

* Active and Passive transport across the membrane.

Passive transport:- The movement of a solute across the membrane from its higher conc. region to its lower conc. region. It is associated with free energy change (ΔG) negative.

Active transport :- The movement of a solute species against its conc. gradient is called A.T. Here ΔG is +ve.

Passive transport is thermodynamically favoured.
Active " needs to be coupled with another thermodyna-
-mically favoured process to make the resultant ΔG -ve.
∴ generally ATP hydrolysis is coupled with an A.T. system
($\Delta G = -30.5$ KJ/mol).

Ion-Transport:-
The charge transport is a very imp. It is mainly done by H^+, Na^+, K^+, Mg^{+2} and Ca^{+2}.
All the required free energy for life process comes from

election transfer process:- $O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$

→ It gives ≈ 0.6 m mol of e^- per second.
→ equivalent to 60A of current in a Resting human.
→ It occurs through ionic conduction

Cell membrane are composed of double layers of protein separated by lipids. Cations cannot pass through the lipid bilayer membrane and these are carried by the specially designed carriers whose outer surface is hydrophobic and lipid soluble.

The ions are distributed across the membrane in such a fashion that electroneutrality is maintained on both sides. by Cl^-, HCO_3^-, SO_4^{2-}, PO_4^{3-}.

Extracellular fluid: (ECF) = Na^+ (0.15), K^+ (0.005)
Intracellular fluid: (ICF) = Na^+ (0.01), K^+ (0.15)

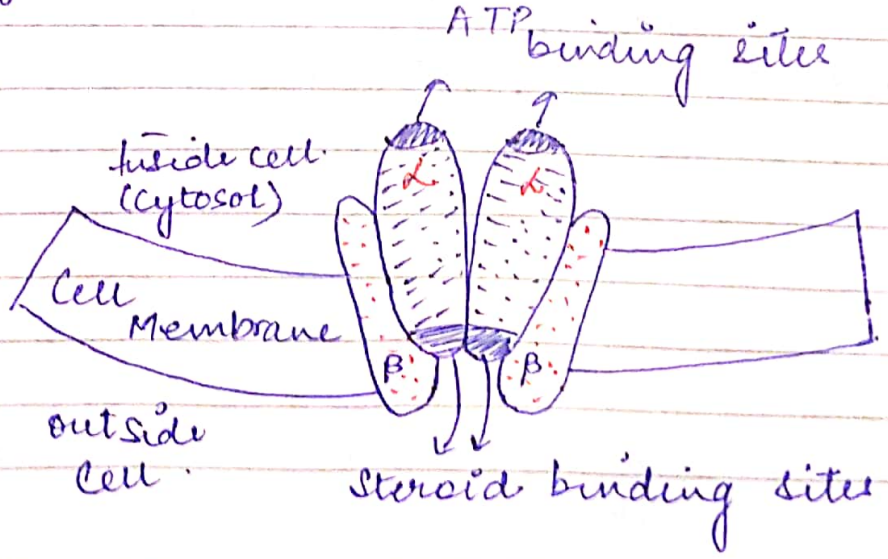
SODIUM POTASSIUM PUMP:-

In order to maintain the cell potential, cells must keep a low conc. of sodium ions and high levels of K^+ ions with in the cell. outside the cell there is high conc of Na^+ & low conc. of K^+, so diffusion occurs through ion channels in the plasma membrane.

The concentration gradients for Na^+ and K^+ ions are maintained by the Na^+-K^+ pump driven by an integral enzyme known as Na^+-K^+ ATPase (M.W = 280 KDa)

This enzyme ($\alpha_2\beta_2$ tetramer) has two α-subunits (M.W 100KDa)
two β- subunits (M.W ≈ 40kDa)

The larger unit α_2 - contains ATP binding site

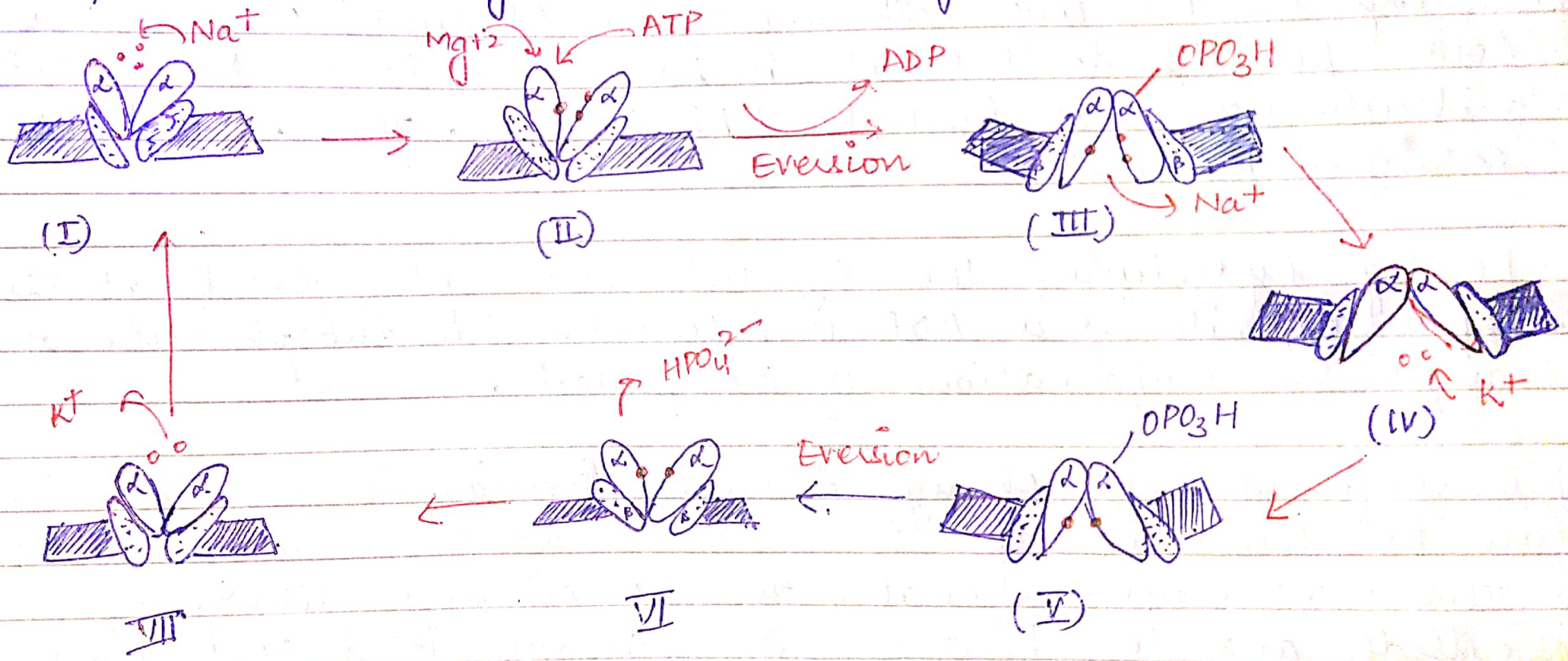


Schematic represent of $\alpha_2\beta_2$ of Na^+-K^+-ATPase.

In the function of pump the α_2 units actually acts as revolving door

The α - chain contain the selective metal binding site and phosphorylation site. They traverse the plasma membrane

The β - chain mainly contain carbohydrate.



The overall process is:-

$$3(Na^+)_{in} + 2(K^+)_{out} + MgATP^{2-} + H_2O \longrightarrow 3(Na^+)_{out} + 2(K^+)_{in} + MgADP^- + HPO_4^{2-} + H^+$$

Functioning

→ One cycle involves the transport of $3 Na^+$ ions from inside the cell to outside the cell and $2K^+$ ions from outside the cell to inside the cell.

→ Binding of $3 Na^+$ ions with the protein (α_2 unit) changes the local polarity so that it is favourable to bind an ATP molecule which is hydrolysed by ATP-ase. This hydrolysis is catalysed by Mg^{+2}.

→ During hydrolysis, the α_2-unit is phosphorylated at the aspartate site and ADP is released. This phosphorylation changes the conformation of the protein.

→ This conformational change is called Eversion (whose function can be compared with the motion of a revolving door). In this new conformational, the Na-binding sites become open to outside and the binding sites cannot bind Na^+ ions as strongly as before.

→ This leads to the release of Na^+ ions to the ECF.

Then the open channel binds $2K^+$ ions from outside and this binding causes dephosphorylation from the protein chain.

This dephosphorylation causes an Eversion which opens the K^+ binding sites open to ICF. In this conformation K^+ is not bound as strongly as before and as a result K^+ ions are released into ICF.

→ Now this leads to the original conformation ready to take up the Na^+ ions to initiate a new cycle.

* It is noted that vanadate (VO_4^{3-}) even at extremely low concentration can inhibit the function of $Na^+ - K^+$ pump. VO_4^{3-} and PO_4^{3-} are structurally similar ∴ it can compete with PO_4^{3-}.
Now it is known that removal of PO_4^{3-} through hydrolysis can occur easily and in fact this dephospholylation causes Eversion to change the conformation.
But if VO_4^{3-} is bound to the aspartate moiety, then its removal through hydrolysis cannot occur to carry out the eversion and consequently the bound K^+ cannot be released.