* the goal of pharmacotheraputics is to achieve a desired beneficial effect with the minimal adverse effect possible.

* the clinician must determind the dose (that achieve the goal)

* fundamental hypothesis → relationship exist between beneficial or toxic effect of a drug and the concentration of it in the site of action or the blood.

* the drug needs to reach the site of action ⟹ has to passage throw membrane

By 4 methods

→ lipid diffusion
- most important mechanism
- passive diffusion (should be)
  - No power required
  - No carrier required

→ So it is moving upon concentration gradiant and the blood will always circulate the drug so it will never reach equilibrium and will be fully diffusied to the cell.

→ it will be upon Fick's law because it is Diffusion

$$\text{flux} = \frac{(C_1 - C_2) \cdot \text{permeability coefficient}}{\text{thickness}}$$

(C_1: higher concentration; C_2: lower conc. and usually is zero in beginning)

Unit: molecule / unit time

thickness → thickness or the length

* more lipid soluble = more passage across membrane

→ it has to be
- lipid soluble (to dissolve in membrane)
- water soluble (to reach membrane)

* So most drug are → weak acid / weak base

* Pka and pH of medium will affect lipid solubility

* How? remember all acid or base is exist in two forms

- protonated
  - acid ($R-COOH$) → it is NOT ionized
  - Base ($R-NH_3^+$) → it is ionized
- not protonated
  - acid ($HCOO^-$) which is ionized (has charge)
  - Base ($R-NH_2$) which is NOT ionized

* ionized → polar → water soluble

* NOT ionized → not polar → lipid soluble

So By Henderson equation we can chang status of acids:

$$\underbrace{R-COOH}_{\text{lipid soluble}} \rightleftharpoons \underbrace{R-COO^-}_{\text{water soluble}} + H^+$$

and bases:

$$\underbrace{R-NH_3^+}_{\text{water soluble}} \rightleftharpoons \underbrace{R-NH_2}_{\text{lipid soluble}} + H^+$$

the equation is:

$$\log \frac{[\text{protonated}]}{[\text{unprotonated}]} = pka - pH$$

Example:

weak base drug with pka of 7 what is the proportion of ionized and unionized drug in blood (7.4) and Urine (pH = 6):

Ans: in Blood:

$$\log \frac{[\text{protonated}]}{[\text{unprotonated}]} = pka - pH$$

$$= 7 - 7.4$$

$$\log \frac{[\text{protonated}]}{[\text{unprotonated}]} = -0.4$$

$$\frac{[\text{protonated}]}{[\text{unprotonated}]} = 10^{-0.4} = \frac{0.4}{1}$$ (protonated / not protonated)

* so protonated = $\frac{0.4}{1.4} \rightarrow 0.4$ of 1

* in Urine:

$\log \frac{[\text{protonated}]}{[\text{unprotonated}]} = 7-6 \Rightarrow \log \frac{[\text{prot}]}{[\text{unprot}]} = 1 \Rightarrow 10^1$ so $\frac{[\text{prot}]}{[\text{unprot}]} = \frac{10}{1}$

* so the drug is protonated and because it is weak base it is ionized so it won't Be absorbed unless I change the pH of the intistine.

Another example:

phenobarbital is weak acid drug with pka of 7.4.

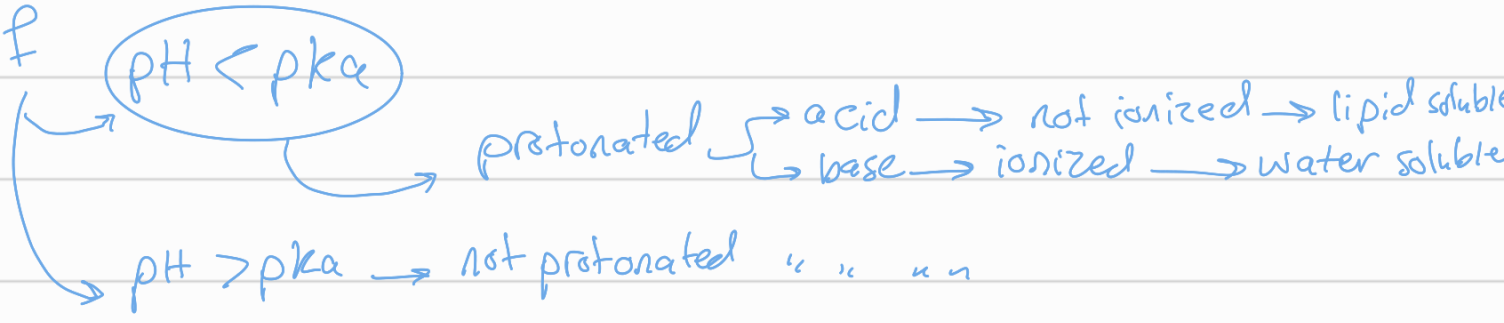
what is the proportion of ionized and unionized drug in Blood and Urine ? Ans: $\log \frac{[\text{prot}]}{[\text{unprot}]} = \text{pka} - \text{pH}$ So in the Blood

$\log \frac{[\text{prot}]}{[\text{unprot}]} = 7.4 - 7.4 \Rightarrow \log \frac{[\text{prot}]}{[\text{unprot}]} = 0 \Rightarrow \frac{[\text{prot}]}{[\text{unprot}]} = 1$ so 1:1 =

in Urine $\log \frac{[\text{prot}]}{[\text{unprot}]} = 7.4 - 6 \Rightarrow 10^{1.4} = \frac{25}{1} \Rightarrow 25:1$ [prot] : [unprot]

so it will be protonated and because it is acid

it will be not ionized so will be reabsorbed to intistine.



* acid in acidic enviroment is not ionized and base in Basic enviroment is also unionized. and vice versa ⇒ acid in Bacic enviroment is ionized

* Applications: Manipulation of Drug execretion by the kidney

So we can transform drug from unionized form to ionized to stop absorbtion by changing pH → for Alkaline Urine → Sodium BiCarbonate ($NaHCO_3$)

→ for acidic Urine → Vitamins C or NH_4Cl

ascorbic acid

will go Back to 4 ways the drug can enter the cell.

2. Aqueous diffusion (By Conc. gradiant)
throw aqueous pores and exist in

- larger Compartments
  - interstitial space
  - cytosol
- tight junctions
- endothelial lining of Blood vessels

* drugs bound to plasma protein
Can NOT use this method because it will be larg
* if the drug was charged it will move also upon electrical fields (membrane potential)

3. Special carriers

- two larg molecule
- two insoluble in lipid

as peptides, Amino acids, glucose

* they bring drug movement by
  - active transport
  - facilitated diff.

* so they selective, saturable and inhibitable

Transporters
that expelling molecule
(prevent it from enterance)

ATP Binding cassette
(ABC family)

P-Glycoprotein or (the same thing but different names)
multi drug resistanse Type1 (MDR1)

- Brain
- intestine
- Testes
- neoplastic cell

Multidrug-resistanse associated protein (MRP)
* also from ABC family
* play role in execretion of drug and their metabolites into Urine and bile
* mediate the resistance of some tumors to chemotheraputic agent

the Solute Carrier families (SLC)
* they do not use ATP but use ion gradiant for transport energy.
* important in transport or uptake the neurotransmitters across nerve ending membranes.

the last way of the 4 ways is Endocytosis and Exocytosis

* it is very specific way. and it is active transport

such as

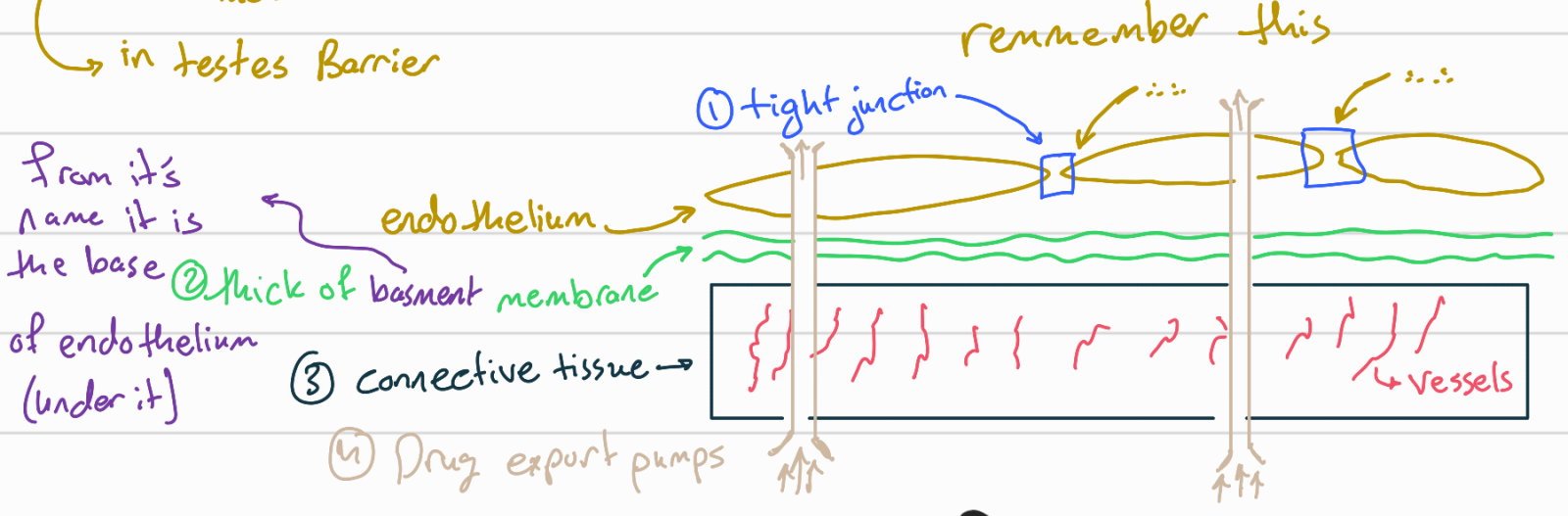
- transport of vitamins B12 complexes with intrinsic factor across the wall of the gut to the Blood
- and iron associated with transferrin into RBCs

Exocytosis: execretion of neurotransmitter Hormons

* these principles of permeation of drug apply to drug → Absorbtion, distribution, elimination and determine how Rapidly and How long these drugs will appear in the site of action and organs of elimination.

* Barriers Against Drug permeation & transport
  - tight junction between endothelial cells and absence of pores
  - presence of thick Basment membrane
  - presence of Connective tissue such as astrocytes in Brain
  - presence of Drug export pumps.
  - presence of intracellular and extracellular enzymes which metabolise drug

as in
- endothelial cell of Blood Brain Barrier
- in testes Barrier



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