* SHEET 7 *

* How the drug moves from the site of administration to the systemic circulation:-

1. lipid diffusion
2. aqueous diffusion
3. special carries
   - A. ABCs
   - B. MDP
   - C. SLC
4. endocytosis and exocytosis ..

2. aqueous diffusion:-

* transport ions and small molecules through aqueous pores within the membrane
* facilated diffusion →
  - Ions → electochemical gradients.
  - small molecules → concentration gradient.
* occures in larg aqueous component
  - interstitial fluid
  - cytosol
  - endothelial cells lining blood vessels.
* drugs that are bound to Plasma proteins don't pass through aqueous carriers.

3. Special carriers:-

* used to transport molecules that are insoluable in lipids but soluable in water and essintial for the cell [Glucose, Amino acid and peptides]
* Selective → each substance has it's own carrier
* passive vs Active
* e.gs: ABCs / MDP / SLC

A. ABCs + MDP:-

* tumer → cancer cells → growing in petridish → certain drug → initially → cancer cells will be killed

observe that there is resistance against the drug and any similar drug

HOW?! → by using ATP [against its concentration gradient]

* they notice that the cancer cells produce P-GLYCOPROTEINS or Multidrug-resistance transpo (MDR1) which functions to efflux the drug from the cell before to do any effect inside.
* benfical mechansim → getting out of toxins outside the cells.
  bad mechansim → adaptation of cancer cells against the chemothraputics agent and some bacteria to the antibiotics.

B. SLC: solute carriers proteins:-

* passive faciliated diffusion
* reuptake for the neurotransmitters from the synaptic cleft to the pr-synaptic neuron.

3. endocytosis and exocytosis

* for larg molecules ether water soluable or lipid soluable
* induced by endocytosis-induced receptors. ⇓ needs Ca^{+2} ions
* e.g:-
  1. vitmin B12 is complexed with internsic factor secreted by stomach cells → ileum to be absorped there
  2. transferrin ion → receptor-induced endocytosis → englufment into the RBCs → iron inside the cell and the transferrin
     - → degradation by lysosomal enzymes
     - → exsit the RBCs and can be reused again.

e.gs:

1. placental barrier → seperation between the maternal and the fetal circulation
2. testies barrier → preventing the mol to get in
3. blood-Brain barriers.

* Barriers against permeation of Drug and transport:-
  - tight junctions between endothelial cells
  - the presence of thick basment membrane. thickness ↑ so permeation ↓ * Fick law of diffusion *
  - presence of C.T under the basement membrane
  - the presence of ABCs and MDP
  - the presence of intracellular and extracellular enzyme → digestion of the drug.

First-pass effect - (First pass metabolism) - (pre systemic metabolism):-

* First pass effect:- the route of the drug from the site of adminstration to the systemic circulation.

orally:- intestinal lumin → intestine wall → portal circulation → liver → systemic circulation

* organs of metabolism:-

1. the LIVER [highest metabolic activity]
2. intestin [less efficacy]
3. endothelial cells of the portal circulation [less efficacy]
3. hair follicels [less efficacy]

* the amount of the drug that will ~~release~~ recieve the systemic circulation is decreased due to the first pass effect. (metabolism of the drug) → and do not do the therapeutic effect before reaching the systemic circulation). So what is the solutions?

1. increasing the dose ~~with~~ in propotion with first pass effect
   e.g: if the FPM = 50% from the drug normal dose = 50 mg so we increase the dose to 100 mg to acheive the therapeutic effect
2. chang the site of adminsteration to a site where the first pass effect is less
   e.g: orally → IV
3. drug with no First pass effect
   e.g:- patients with liver cherosis they have (shunting blood)
   - no first pass effect - blood → portal circulation → systemic circulation without metabolism from the liver.
   decrease the dose → avoiding toxicity.

* Bioavailability:-

* the fraction of the drug that is received to systemic circulation.
* bioavailability might be
  - → 1 or 100% [IV]
  - → less than 1 ?
    - → first pass metabolism
    - → manufacturing
    - → manufacturing dosage
    - → ~~hepato~~ Enterhepatic circulation
    - → distruction by GIT gastric acid or bacteria.
    - → absorption.

* the drug is very hydrophilic (atenolol) → soit canot ~~reach~~ pass the plasma membrane
* the drug is very lipophilic → soit cannot reach ~~to~~ or move to reach the plasma membrane (acyclovire)

* ABCs and MDP:- P-Glycoprotein which efflux the drug outside the ~~tood~~ cell befor doing its effect.

1. absorption phase:- absorption rate > elemination rate
2. peak: absorption = elemination rate
3. + 4. elemination rate > absorption rate

لازم الجرعة إلى تتاخذ تكون بحيث التأثير إلى بدي إياه بدون ما أوصل للـ toxicity. وما تكون قليلة كثير.
مثلاً لو الدوا بتاخذ على شكل ٣ حبات بـ اليوم يكل مرة حبة الـ (يعني حبة كل 8 ساعات) ← بكون الدوا تركيزه قريب من MEC بعد 8 ساعات فياخد الجرعة الثانية عشان يضل تركيز الدوا فعال بجسمه

* Bioavailability can be measured by the area under the curve:-