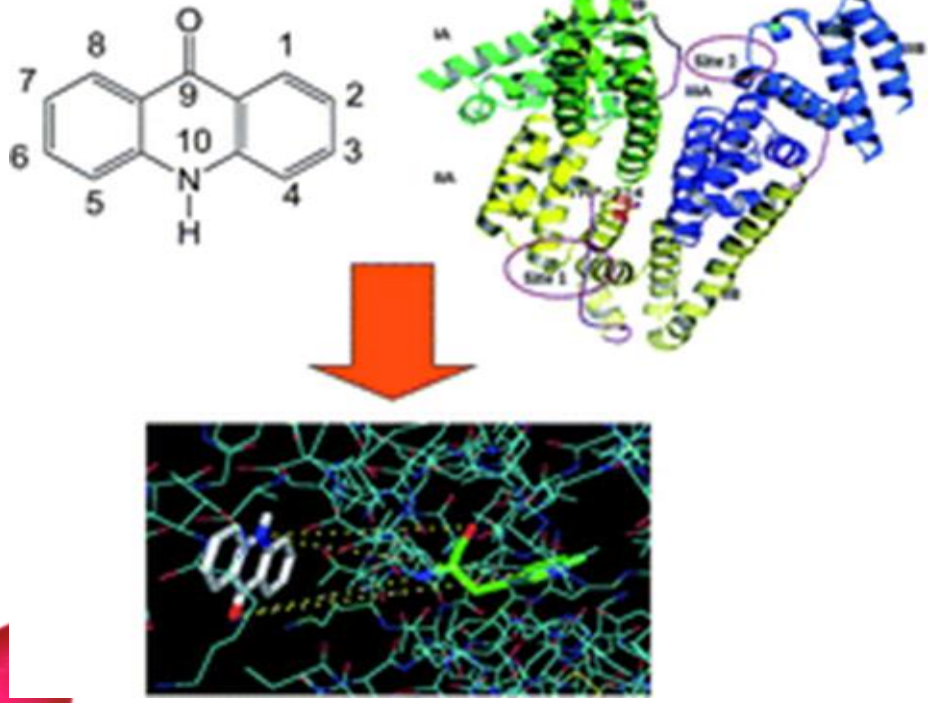


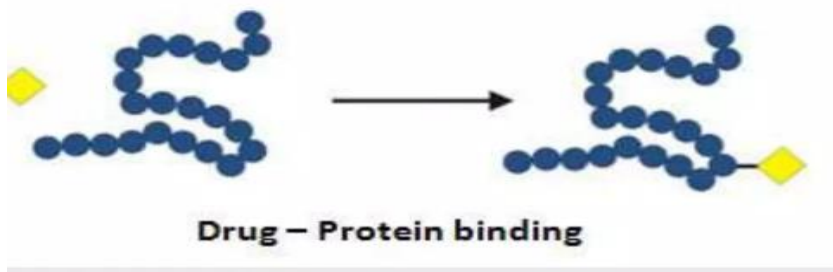
PROTEIN BINDING OF DRUGS

PUNITHA S
PHARM D IV YEAR
BIOPHARMACEUTICS AND PHARMACOKINETICS.

INTRODUCTION:

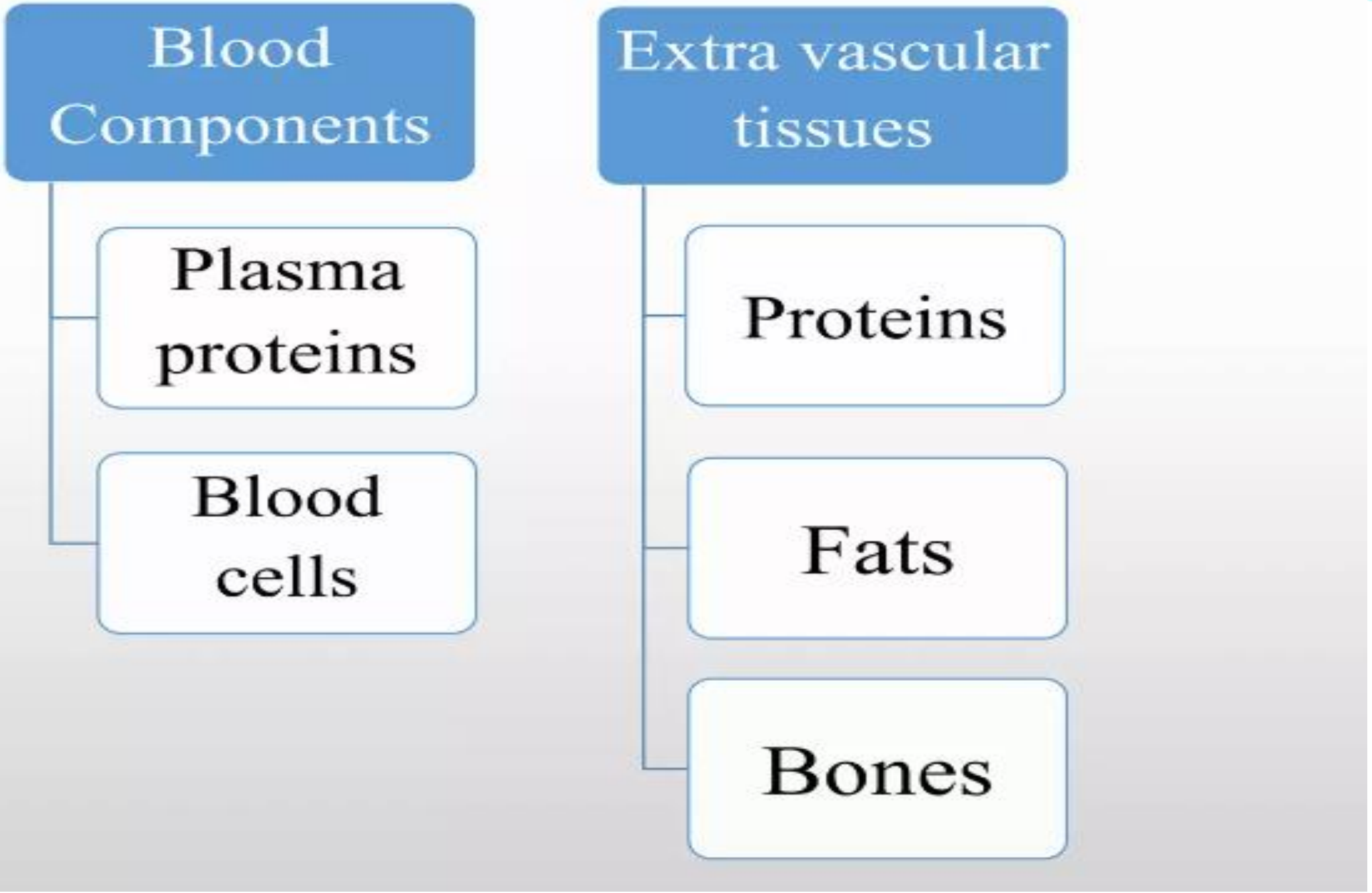
Drug interact with several tissue components of which the two main categories are:

1. *Blood*
2. *Extravascular tissues*



Interacting molecules are generally macromolecules such as proteins,DNA etc..

The phenomenon of complex formation with proteins is called protein binding of drugs.


Blood Components
Plasma proteins
Blood cells
Extra vascular tissues
Proteins
Fats
Bones

MECHANISM OF PROTEIN DRUG BINDING

Binding of drugs to proteins is generally reversible.

- ✓ Reversible generally involves weak chemical bonds such as

  1.Hydrogen bonds

  2.Hydrophobic bonds

  3.Ionic bonds

  4.Vander Waal's forces.

- ✓ Irreversible drug binding though rare, arises as a result of covalent binding and is often a reason for the carcinogenicity or tissue toxicity of the drug.

BINDING OF DRUGS TO BLOOD COMPONENTS

PLASMA PROTEIN –DRUG BINDING:

- The binding of drugs to plasma proteins is reversible.
- The extent or order of binding of drug to plasma protein is

  Albumin > A1 acid gp > lipoproteins > globulins

BINDING OF DRUGS TO HUMAN SERUM ALBUMIN:

- It is the most abundant plasma protein (59%) having M.W of 65000 with large drug binding capacity.
- Both endogenous compounds such as fatty acids ,bilirubin as well as drug binds to has Four different sites for drug binding:

  Site 1: Warfarin & azapropazone binding site.

  Site 2 :Diazepam binding site.

  Site 3: Digitoxin binding site.

  Site 4: Tamoxifen binding site.

BINDING OF DRUGS TO ALPHA – 1 ACID GLYCOPROTEIN(orosomucoid) :

It has M.W of 44000 and plasma conc.range of 0.04 – 0.1 g%.It has bind to a no. of basic drugs like imipramine ,lidocaine, propranolol and quinidine.

BINDING OF DRUGS TO LIPOPROTEINS :

- Binding occurs by hydrophobic bonds.MOL.WT of 2 – 34 lacks Dalton.
- Lipid core composed of

  Inside : triglyceride & cholesteryl esters

  Outside : apoprotein.

E.g: Acidic : Diclofenac

Neutral : Cyclosporin A

Basic : Chlorpromazine

BINDING OF DRUGS TO GLOBULIN:

GLOBULIN	SYNONYM	BINDS TO
α1GLOBULIN	Transcortine/ corticosteroid binding globulin	Steroidal drugs,Thyroxin & Cyanocobalamine.
α2GLOBULIN	Ceruloplasmine	Vitamin A,D,E,K.
β1GLOBULIN	Transferin	Ferrous ions
β2GLOBULIN	---	Carotinoids
γGLOBULIN	---	Antigens

BINDING OF DRUGS TO EXTRAVASCULAR TISSUE

The body tissues ,apart from HSA ,comprise 40% of body weight which is 100 times that of HSA . Hence tissue – drug binding is much more significant than thought to be.

Importance :

1. It increases apparent volume of distribution.
2. Localization of a drug at a specific site in body.

Factors affecting : Lipophilicity , Structural feature of drug , perfusion rate , pH differences.

Binding order :

Liver > Kidney > Lung > Muscles .

BINDING OF DRUGS TO BLOOD CELLS

In blood 40% of blood cells of which major component is RBC (95%).RBC is 500 times in diameter as the albumin .The rate and extent of entry into RBC is more for lipophilic drugs.RBC comprise of three components.

a) HAEMOGLOBIN : It has a MW of 64,500 Dal.Drugs like phenytoin ,phenobarbital bind to haemoglobin.
b) CARBONIC ANHYDRASE : Carbonic anhydrase inhibitors drugs are bind to it like acetazolamide and chlorthalidone.
c) CELL MEMBRANE : Imipramine & Chlorpromazine are reported to bind with the RBC membrane.

TISSUES	Binding of
1. Liver	Irreversible binding of Epoxides of halogenated hydrocarbon and paracetamol.
2. Lungs	Basic drugs : Imipramine , Chlorpromazine and Antihistaminics
3. Kidney	Metallothionin protein binds to heavy metals & results in renal accumulation and toxicity.
4. Skin	Chloroquine and Phenothiazine binds to melanin.
5. Eye	Chloroquine and Phenothiazine also binds to Eye melanin and results in retinopathy.
6. Hairs	Arsenicals,Chloroquine & Phenothiazine.
7. Bones	Tetracycline (yellow discoloration of teeth),Lead (replaces Ca & cause brittleness).
8. Fats	Lipophilic drugs (thiopental),Pesticides (DDT).
9. Nucleic acids	Chloroquine & Quinacrine

COMPARISON BETWEEN PLASMA PROTEIN-DRUG BINDING AND TISSUE-DRUG BINDING

S.NO	PLASMA PROTEIN-DRUG BINDING	TISSUE-DRUG BINDING
1	Binding involves weak bonds and thus reversible.	Binding involves strong covalent bonds and thus irreversible.
2	Drugs that bind to plasma proteins have small apparent volume of distribution.	Drugs that bind to extravascular tissues have large apparent volume of distribution.
3	Half life of plasma protein bound drug is relatively short.	Half life of extravascular tissue bound drug is relatively long.
4	Does not result in toxicity.	Tissue toxicity is common.
5	Displacement from binding sites is possible by other drugs.	Displacement by other drugs generally does not occur.
6	Competition between drugs for binding to plasma proteins can occur.	Tissue-drug binding is generally non-competitive.

FACTORS AFFECTING PROTEIN – DRUG BINDING

Drug related factors:

a) Physicochemical characteristics of drug.

b) Concentration of drug in the body.

c) Affinity of drug for a particular binding component.

Patient related factors:

a) Age

b) Intersubject variations

c) Disease states.

Protein/Tissue related factors:

a) Physicochemical characteristics of protein or binding agent.

b) Concentration of protein or binding component.

c) Number of binding sites on binding agent.

Drug interactions:

a) Competitions between drugs for the binding site.

b) Competition between drug and normal body constituents.

c) Allosteric changes in protein molecule

DRUG RELATED FACTORS

a) Physicochemical characteristics of drug

Protein binding is directly related to the lipophilicity of the drug. An increase in lipophilicity increase the extent of binding.

b) Concentration of drug in the body

Alteration in the conc. Of drug substance as well as the protein molecules or surfaces subsequently brings alteration in the protein binding process.

c) Affinity of drug for a particular binding component

This factor entirely depends on the degree of attraction or affinity the protein molecule or tissues have towards drug moieties.

For digoxin has more affinity for cardiac muscles proteins as compared to that of proteins of skeletal muscles or those in the plasma like HSA.

Protein/ tissue related factors:

a) Physicochemical characteristics of protein or binding agent:

•Lipoproteins & adipose tissue tend to bind lipophilic drug by dissolving them in their lipid core.

•The physiological pH determines the presence of active anionic & cationic groups on the albumin to bind a variety of drug.

b) Concentration of protein or binding component:

• Among the plasma protein , binding predominantly occurs with albumin, as it is present in high concentration in comparison to other plasma protein.

• The amount of several proteins and tissue components available for binding, changes during disease state.

DRUG INTERACTIONS

a) Competition between drugs for the binding sites [Displacement interactions]:-

$$D1+P \xrightarrow{D2} D2+P$$

D1:Displaced drug. D2: Displacer drug.

Eg. Administration of phenylbutazone to a patient on Warfarin therapy results in Hemorrhagic reaction.

b) Competition between drug & normal body constituents:-

The free fatty acids are known to interact with a no. of drugs that binds primarily to HSA. the free fatty acid level increase in physiological, pathological condition.

c) Allosteric changes in protein molecule:-

The process involves alteration of the protein structure by the drugor it's metabolite there by modifying its binding capacity.

Eg. aspirin acetylates lysine fraction of albumin thereby modifying its capacity to bind NSAIDs like phenylbutazone.

Patient-related factors

a) Age:

1.Neonates: Low albumin content: More free drug

2.Young infants: High dose of Digoxin due to large renal clearance.

3.Elderly:Low albumin: So more free drug.

b) Intersubject variability:

Due to genetics & environmental factors.

c)Disease state

Disease	Influence on plasma protein	Influence on protein drug binding
Renal failure	↓ Albumin content	↓ binding of acidic drugs; neutral and basic drugs are un affected
Hepatic failure	↓ Albumin synthesis	↓ binding of acidic drugs; and binding of basic drugs is normal or ↓ depending on AAG levels
Inflamatory states i.e,truama surgery etc…	↑AAG levels	↑ binding of basic drugs; neutral and acidic drugs are un affected


Thank You!