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Plasma proteins 2

Polymorphism: poly= many morph = form

When mutation occur in the DNA level, it changes the amino acid sequence in the protein so the protein is changed. It will be pathological or non-pathological. This mutation transmits from parents to children and start increase more and more. When the percentage of this mutation reaches 1% or more in population, we call it "polymorphism".

Some examples:

1) ABO blood group: the most common type of blood group is: O. (A, B, AB) they are less common but they are over 1% of population got it so they are polymorphism.
2) Eye colour.

Many plasma proteins are polymorphic proteins so they exist in different copies in different people. a1-antitrypsin, haptoglobin, transferrin, ceruloplasmin, and immunoglobulins are examples of polymorphic plasma proteins.

How we can detect these proteins?

1) By use electrophoresis: because the sequence of amino acids is changed so the size is changed as a result.
2) By using isoelectric focusing: the changed amino acids may be charged so we can use this technique.

Plasma proteins half-lives:

What is half-life:

The time that needed to reach the half of the concentration of a protein.

How can we know the half-life for proteins?

It can be determined through **isotope labelling studies** (I-131). Label protein with (I-131), introduce it into the body, keep watching it until it reaches the half concentration of the original concentration then determined the half-life.

Note: plasma proteins vary in their half-lives.

Memorize the following numbers: half-life for **albumin is 20 days** and half-life for **haptoglobin is 5 days**

Why it is important to know half-lives for plasma proteins?

For diagnosis reasons.

Example for disease result in decrease the half-lives for proteins:

In cases of general diseases such as (protein losing gastro enteropathy) which effect the GI system (inflammatory chronic diseases). In effected area we find inflammation that means blood vessels become wider (more blood come to it). The spaces between cells increase so the filtered amount from blood to outside will also increase making a swelling in that area, so we loss proteins.

Functions of plasma proteins:

General functions:

1) **contributes to blood viscosity:** any substance that dissolve in water make it more viscous and plasma proteins are globular proteins which is soluble in water.

2) **Maintenance of blood pH** (Amphoteric property): they work as buffers because all proteins have a free carboxylic group (-) and free amine group (+) and that's why all proteins work as buffer in any solution.

3) **Nutritive role:** not all plasma proteins transport nutrition elements but when we need energy we can break down any protein we want.

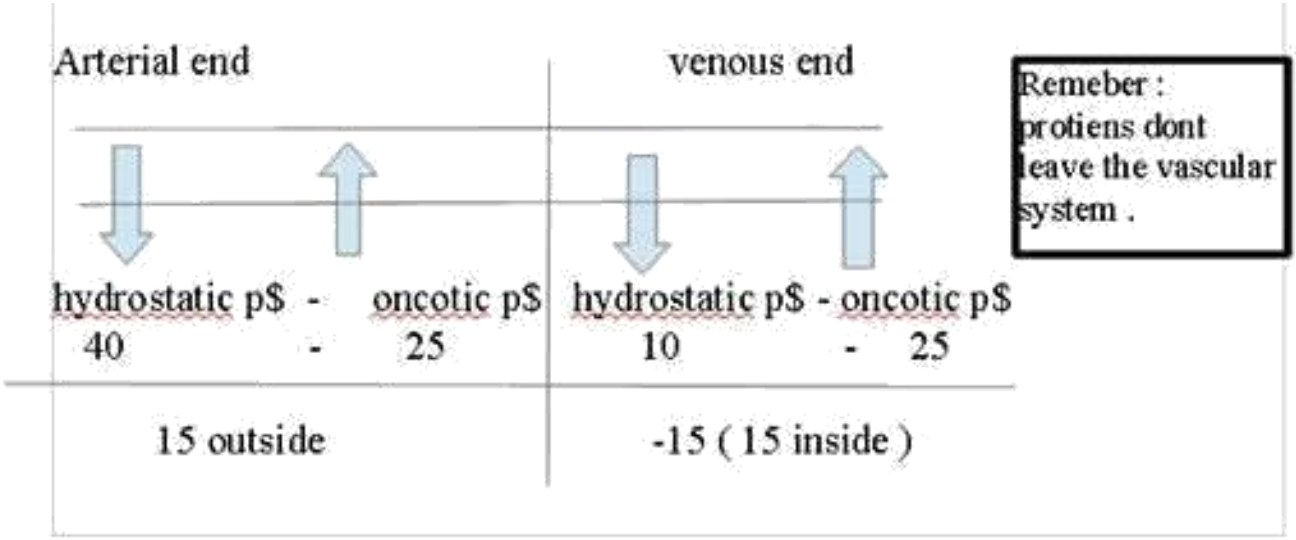
4) **Maintenance of blood pressure:**

the forces which affect the capillary are called starling forces:

1- oncotic (osmotic by proteins) pressure: favours the water to come in caused by the protein (return water).

2- hydrostatic pressure (blood pressure: the pressure acting on the wall of vessels): favours the water to come out with nutrition elements.

note: proteins don't leave the vascular system



In case of liver failure: plasma proteins will decrease. the oncotic pressure will decrease. In the previous example: suppose the oncotic pressure 20 instead of 25 we will get this results:

in arterial end

40-20 =20

In Venous end

10-20= -10

more fluid will come out and less fluid will come in. and this cause **Edema**

Acute-phase proteins

proteins will **increase** dramatically in their **concentration** (up to 1000 folds) in cases of acute inflammation, chronic inflammation and cancer.

These proteins are: CRP / C reactive protein, a1-antitrypsin, haptoglobin, Fibrinogen. (memorize them, common question in exams)

How these proteins increase?

interleukin-1 (is a cytokine) binds to receptors on the liver cell surface. This binding activates **NFKB** (nuclear factor kappa -B) which is a **transcription factor** exist in cytosol in an inactive form.

After binding it will have activated and trans-located to nucleus. NFKB is a **transcription factor** which binds to DNA that means more mRNA, more translation and more proteins (Increasing in their concentration).

Common questions:

1) What induces NFKB?
2) What is the action of NFKB?
3) What is the action of interleukin-1?

Negative acute phase proteins: albumin, prealbumin, transferrin. (their concentration doesn't change or may be decreased).

Question: which one of the following **doesn't have polymorphic forms:**

A)ceruloplasmin
B)transferrin
C)haptoglobin
D)transthyretin
E)immunoglobulin A

Answer is D

QUESTION: which one of the following **is an acute phase protein:**
A)fibrinogen
B)transferrin
C)albumin
D)transthyretin

Answer is A

QUESTION: which one of the following **is true about NFKB functions:**

A)while being in the cytosol
B)after trans-located to the cytosol
C)stimulates Interleukin 1
D)activates gene transcription

Answer: D

Now we will talk about plasma proteins one by one:

Albumin:

It synthesized as a preproalbumin then it will lose the signal peptide to become proalbumin then it will lose a hexapeptide (6 amino acids) to form fully active albumin with a specific final shape. It has 3 big domains: (1A-1B) / (2A -2B) / (3A-3B). Each domain will have a certain function, for example: one of these domains is called "albumin binding domain" and its function is to bind.

The most important thing about Albumin: it works in **transport**, **transporting** a lot of material in the blood.

The Major Protein in Human Plasma, 69 kDa, half-life (20 days). The main contributor to the osmotic pressure (75-80%). One polypeptide chain, 585 amino acids, 17 disulfide bonds (the final form is stable and the shape is fixed and shouldn't change easily).

Liver produce 12 g of albumin per day. 25% of the total protein synthesis.

How we can use this thing in clinical application?

If the concentration of albumin in the blood is decreased, there is a problem in the liver (so it works as a **liver function test**). But there is a problem because the half-life of albumin is long (20 days).

Ellipsoidal shape: we discuss this point in the previous sheet.
It carries 20 negative charges so it is highly negative.

Binds to a lot of materials:

Free fatty acids (FFA), Certain steroid hormones, Bilirubin, Plasma tryptophan, Metals:(Calcium, copper and heavy metals), Drugs: (sulfonamides, penicillin G, dicumarol, aspirin) (drug-drug interaction)

Drug-Drug interaction:

Albumin is the site of bind many drugs so logically we should find

to drugs that bound to the same site on albumin. The drug with the higher concentration and higher affinity will cause dissociation of the other drug, and accordingly will cause more effect of the dissociated (free) drug.
(important note: the effect is from the free drug, not from the bound one)

1) **Bilirubin-Aspirin interaction:**

Bilirubin is produced from the breakdown of heme, which takes place in the process of hemoglobin degradation. It is taken to liver so if the liver has a problem, Bilirubin go outside the liver to tissues, so its colour become yellow. There is no maturity enough to deal with Bilirubin in new-borns and it needs a week to deal with it.

-It is not allowed to give new-borns aspirin; because aspirin binds to the same place where Bilirubin binds on albumin.

If you give aspirin to the new-born, **aspirin has higher affinity** than Bilirubin to bind with albumin, more Bilirubin will be dissociated of albumin. Bilirubin gets out of the circulation to the brain easily in new-borns since the blood brain barriers (BBB) is not acting well, the presence of Bilirubin in the brain is called **kernicterus** and this will cause mental retardation.

2) **Phenytoin-dicoumarol interaction:**

Phenytoin is an antiepileptic drug; it binds to albumin at the same place where dicoumarol binds. **Dicoumarol is an anticoagulant** drug, so giving one of these drugs to a patient will increase with the concentration of the first drug.

Other diseases related to albumin:

Analbuminemia: there is no albumin. Result from genetic disease.

Important point: Analbuminemia cause **moderate** Edema… ***How?***

The concentration of other proteins will increase as Compensatory mechanism not because the need of their function, they will function to prevent the sever Edema.

Hypoalbuminemia: albumin level in blood less than **2 g/dl**

Causes:

1- malnutrition: no proteins in your diet.
2- Nephrotic syndrome
3- Cirrhosis (manly ascites)
4- gastrointestinal loss

We can solve this problem **by removing water.**

Hyperalbuminemia: the concentration of protein may be higher

in cases of dehydration and water loss. (Relative increase not actual increase because liver doesn't change its synthesize rate)

We can solve this problem by drinking of water (hydration)

We finished Albumin

Prealbumin:

It is called prealbumin because it migrates faster than albumin in electrophoresis due to the difference in molecular weight (62 kDa).

Prealbumin functions as a transporter of thyroid gland hormones (T3 & T4) in blood, that's why it is also called **transthyretin.**

properties:

-it has very low concentration (0.25 g/dl)

-it is glycoprotein (unlike albumin)

-short half-life (2 days) what **is the importance of this?** Sensitive indicator of disease, you will not wait 20 days (like the case of albumin). 2 days only.

Globulins:

Three types: alpha, beta, gamma.

Alpha divide into two bands alpha 1 and alpha 2.

In alpha1 we will discuss antitrypsin and fetoprotein.

***Alpha1 -antitrypsin*: main protein in alpha1**

band (90%). -acute phase protein.

-polymorphism protein: different copies in people (M, S, Z, F**).** The

most common and effective one is **M** copy, other copies not functioning well as M copy (in this example polymorphic proteins cause pathological effects). The less active one is ZZ. Everyone has 2 copies of this protein, one M allele at least is required to perform the function.

-Antagonist for many proteases so we call it **α1-antiprotease** or **α1-antiproteinase**.

-one of these proteases is **Elastase** (which break down elastin). Elastin mainly found in lungs.

Macrophages secrets proteases including Elastase to break down pathogenesis and it breaks elastin in normal tissue which can be regenerated.

So where is the problem?

If there is chronic inflammation in the lung, macrophages start secrete Elastase to break down elastin and alpha1 antitrypsin antagonize the action of Elastase. BUT what happen if the antitrypsin doesn't acting well? Elastase will break down elastin in walls of alveoli, so the size of chest will increase and the surface area for gas exchange is decreased and this called **emphysema (one** of its symptoms is **barrel chest** because volume of air increase within the lungs).

The main cause of **emphysema** is smoking. **How?**

It causes oxidation of one of the amino acids residues which are found in a1-antitrypsin. This amino acid is Met358. Methionine is oxidized to methionine sulfoxide. Met358 is very important for the binding of a1-antitrypsin to Elastase. So a1-antitrypsin is no longer able to bind to it, thus Elastase will keep damaging elastin. Imagine person who is smoker and has ZZ polymorphism (disasters case).

Other problems of the ZZ polymorph a1-antitrypsin that it causes cirrhosis. In each ZZ polymorph a1-antitrypsin there are beta sheets and loops, the loop of one ZZ a1-antitrypsin polymorph has high affinity to bind with a beta sheet of another ZZ a1-antitrypsin polymorph. It is so hard to roll around each other in the same a1-antitrypsin polymorph, rather; the loop of one polymorph will bind with beta sheet of other polymorph, and the loop of the second polymorph will bind to a beta sheet of a third polymorph and so on, resulting in **aggregates of a1-antitrypsin**. These aggregates occur in the liver resulting in cirrhosis. 10% of liver cirrhosis cases are caused by a1-antitrypsin deficiency.

Question: which one of the following **doesn't cause emphysema**:
A)SZ
B)MZ
C)FS
D)smoking
E)presence of methionine-sulfoxide at residue number 358

Answer is B

Good luck and sorry for any mistakes ☺