METABOLISM

Doctor 2020 | MEDICINE JU

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**Before we start:
- A mutation is a permanent alteration in at least one nucleotide in the DNA, it might result in a change of one or more amino acids, at also may be harmless (silent mutation).
- Mutations can be common and spread in some societies more than others, so we see variations in the distribution of genetic diseases.
- Not all mutations result in diseases.
-If a certain mutation increased and appeared in more than 1% of certain population (Jordanian people, race, any geographical area), we call it polymorphism (so this change is not rare anymore)
- Polymorphism is simply a change in one or more nucleotides, if a single nucleotide is affected then it's a SNP (single nucleotide polymorphism).

PLASMA PROTEINS AND POLYMORPHISM

A mendelian or monogenic trait

A change in one gene gets inherited by mendelian inheritance until it becomes more prevalent in the population, but it is still called mutation until it exceeds 1% of the population then it is called polymorphism

--BOTTOM LINE: polymorphism isn't always present when talking about genetic alterations, this mainly depends on the gene and the population affect

Exists in population in at least two phenotypes, neither is rare

The ABO blood group are the best-known examples

A harmless polymorphism. O is the most common blood type, while the others are polymorphisms (represented in more 1%)

Also, a harmless polymorphism is the eye color, in Arab world black and brown are common, whereas green and blue are uncommon. In western countries we notice the opposite, so this depends on the population.

α1-antitrypsin, haptoglobin, transferrin, ceruloplasmin and Igs

These proteins exhibit polymorphism (not all have the same amino acid sequence), and this polymorphism may be an indicator of a certain pathology.

Electrophoresis and isoelectric focusing, are used to separate these proteins from each other, depending on certain parameters such as molecular size and isoelectric point (pH point which makes the protein neutral electrically).

PLASMA PROTEINS HALF- LIVES

Proteins like any other substance get continuously degraded and resynthesized in a process known as remodeling, so they inevitably have HALF-LIVES that differ from each other.

Determined through isotope labeling studies(I^{131})

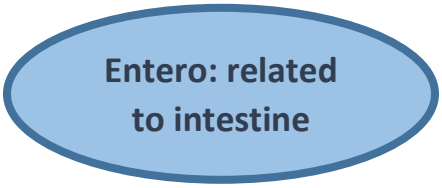
Iodine, as a radioactive element, attaches to proteins, so having got the target protein attached to it, we can measure the initial concentration of protein, followed by serial measurement of concentrations until 50% of the protein molecules is left in the plasma.

Albumin and haptoglobin (20- and 5-days half-lives, respectively)

It also differs whether the protein was bound or free

WHY ARE HALF-LIVES IMPORTANT?
LOOK DOWN!

Diseases can affect half-lives (ex: Crohn's disease), albumin half-life may be reduced (1 day)



PROTEIN LOSING GASTROENTEROPATHY (Crohn's disease is an example of this group of disorders)

Having a chronic inflammation affecting GI tract, signs of inflammation such as redness (because of the increased blood flow) and swelling (because of widening the blood vessels, there will be more space between endothelial cells which line the blood vessel, then plasma exists out of the endothelial lining of the tract accumulating in the extracellular fluid then then plasma proteins will exit the body with feces)

FUNCTIONS OF PLASMA PROTEINS

- SPECIFIC FUNCTIONS (variable between proteins)

enzymes (rennin, coagulation factors, lipases, …)
humoral immunity(immunoglobulins)
blood coagulation factors
hormonal (erythropoietin)
transport proteins(Transferrin, Thyroxin Binding Globulin, Apolipoprotein)

- GENERAL FUNCTIONS

THESE STRONGLY CORRELATE WITH THE NATURE OF THESE SUBSTANCES THAT IS 'PROTEINS', REGARDLESS OF THE PROTEIN'S NAME OR TYPE. Accordingly, they are done by these proteins collectively.

*** A nutritive role**
Like any other protein, plasma proteins are of a nutritive significance, breakable to extract energy. Being similar to fats and collagen as a carbohydrate.

*** Maintenance of blood pH (amphoteric property)**
You know that proteins are composed of one or more polypeptide chains, the single chain has two ends: N-terminus and C-terminus, which are charged. Thus,

they can accept or lose a proton dependent on external conditions, acting as a buffer.

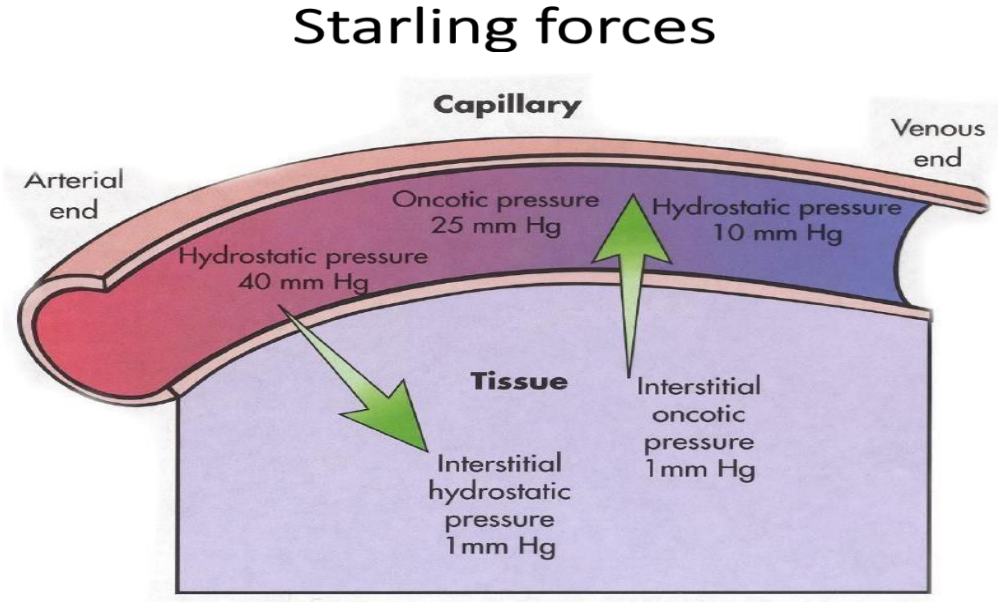
***Contribution to blood viscosity**

Because proteins are soluble, they make the blood viscous (CERTAINLY,TO A LIMIT)

AGAIN, the more the solubility, the more the viscosity.

***Maintenance of blood osmotic pressure (oncotic pressure)**

Proteins are soluble, thus they attract surrounding water molecules and bind to them, by exerting a force on water to keep themselves soluble inside vessels (by hydrogen bonding), so water won't leak outside to the interstitial fluid.



STARLING FORCES: TWO OPPOSITE FORCES CONTROLLING THE EXCHANGE OF NUTRIENTS BETWEEN CAPILLARIES AND TISSUES.

THEY ARE:

1.Oncotic pressure (directs water inside the vessels)

2.Hydrostatic blood pressure (pressure exerted by the fluid in the walls of the vascular system), to the interstitial fluid

Arterioles, venules vs tissue hydrostatic pressure (37,17 vs 1 mmHg)
Plasma proteins oncotic pressure is 25 mmHg
Protein deficiency leads to what??
EDEMA, OFC

Net force on arteriolar side=40-25=15 mmHg OUTSIDE
Net force on venular side=25-10=15 mmHg**INSIDE
**this theoretically results in a zero difference, but the lymphatic system may contribute to an additional 1 or 2 mmHg pressure.

WHY DOES PROTEIN DEFECIENCY LEAD TO EDEMA?
because oncotic pressure reduction or diminishment leads to excessive accumulation of fluids in the interstitial fluid (elevated hydrostatic pressure).

ACUTE PHASE PROTEIN

*Levels increase (0.5-1000 folds), acute inflammation, tissue damage, chronic inflammation & cancer. C-reactive protein (CRP), α1-antitrypsin,haptoglobin and fibrinogen.

*Interleukin 1(IL-1), main stimulator (gene transcription)

They are called acute phase proteins because their conc. raise dramatically upon an acute or chronic inflammation,…

Transcription factor:

a protein involved in the conversion of DNA into mRNA, by binding to specific sequences of DNA like promoter regions, thus producing new proteins

***Nuclear factor kappa-B (NFkB): exist in an inactive form in cytosol, activated and translocated to nucleus (IL-1).**

NEGATIVE ACUTE PHASE PROTEINS: PREALBUMIN, ALBUMIN AND TRANSFERRIN

THE MECHANISM

1. Inflammation activates a molecule (IL-1), which targets liver cells and causes translocation of a transcription factor (NFkB) from the cytosol to the nucleus (inactive to active form).

2.In the nucleus, NFkB binds DNA to start transcription (mRNA), then it became translated producing proteins (plasma proteins), increasing their conc.

Some proteins DECREASE in conc. (or it doesn't change at all), in the aforementioned conditions like albumin, prealbumin and transferrin

Albumin

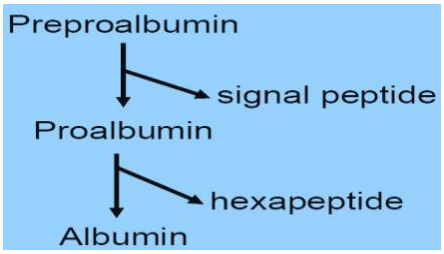
The most frequent plasma protein (55%),
normal range (3.5-5.5 g/dl), the main transporter
- The major protein in human plasma,69 KDa, half-life (20 days)
- The main contributor to osmotic pressure (75-80%).
Surely, because it is the most frequent protein.
- Liver:12 g/day (this constitutes 25% of total protein synthesis in the liver), used in liver function test.

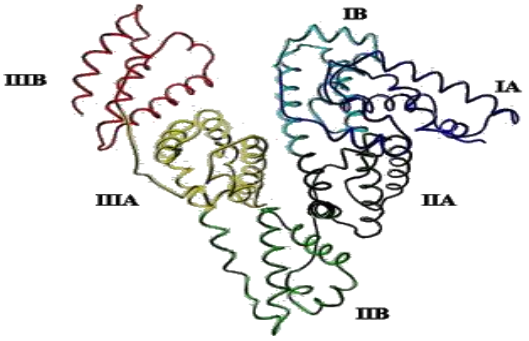
BUT there is a small problem here
Albumin half-life is relatively long (20 days), which means it's not a suitable and enough sensitive indicator for a liver problem (1)

- Synthesized as a preproprotein

After exiting the liver cell, signal peptide separates, resulting in a proalbumin, then proalbumin gets cut (6 amino acids removal)

- One polypeptide chain,585 aa,17 disulfide bonds, proteases subdivide albumin into 3 domains (1A 1B,2A 2B,3A 3B)





-Ellipsoidal shape (VISCOSITY) vs fibrinogen

It's not as much elongated as fibrinogen, thus not as much viscosity.

-Anionic at pH 7.4 with 20 –ve charges.

Albumin binding capacity

Albumin is the major transporter

*BINDS VARIOUS LIGANDS:

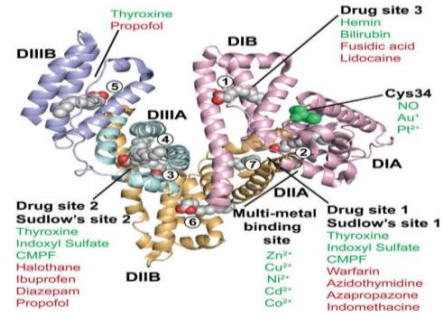
- free fatty acids (FFA)
- Certain steroid hormones
- Bilirubin (a yellow heme-breakage result, responsible for jaundice in skin and sclera)

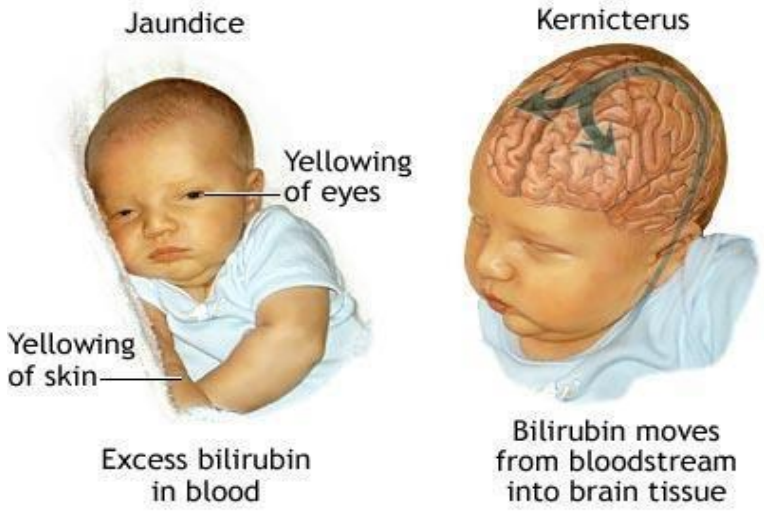
There is a physiological jaundice in newborns, because the processing of bilirubin is not complete (which disappears in almost a week)

- Plasma tryptophan
- Metals: Ca, Cu and heavy metals
- Drugs: sulfonamides, penicillin G, dicumarol, aspirin (drug-drug interaction).

Since almost all drugs bind on albumin, there is a chance of two drugs trying to bind on the same point on the protein, and they will compete with each other according to their affinities and concentration (drug-drug interaction).

One drug will bind and the other one will be free in the plasma (the active one), then it will go to the tissues with fatal concentrations.





--Bilirubin toxicity:
Aspirin is contraindicated in newborns because it binds on the same site as bilirubin (competitive ligand), so giving aspirin to a *newborn will decrease the available binding for bilirubin, so more bilirubin will become free (bilirubin conc. will increase) which enters the immature blood brain barrier, massing in the brain a causing kernicterus-then mental retardation.

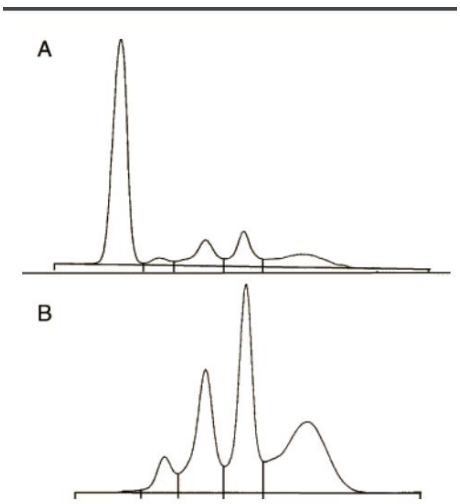
Remember that drugs are effective if they were free not bound to other thing

--Phenytoin & dicoumarol (anticonvulsant & anti-coagulant)
Both drugs have high affinity towards albumin, thus competitiveness increases, leading to significant clinical effects (depending on conc. of both)

---SO THEY SHOULD NOT BE ADMINISTERED TOGETHER---

Other conditions:

1. Analbuminemia



There are human cases of analbuminemia (rare) (a means lack, nal means blood) lack of albumin

Autosomal recessive inheritance

One of the causes: a mutation that affects mRNA-splicing

Patients show moderate edema (not severe because of compensatory mechanism by other plasma proteins)

2. Hypoalbiminemia: conditions where albumin level in blood is less than 2 g/dl and cause edema because of:

Malnutrition (generalized edema)
Nephrotic syndrome
Cirrhosis (mainly ascites)
Gastrointestinal loss

3. Hyperalbuminemia (apparent increasing in albumin level not actual)

Because of dehydration (relative increase)

Prealbumin (transthyretin)

Migrates ahead of albumin, 62 kDa. that's why we call it prealbumin

It is a small glycoprotein (rich in tryptophan, 0.5% carbohydrates)

Blood level is low (0.25 g/L). very low

It has short half-life (≈2 days): sensitive indicator of disease or poor protein nutrition. however there is a problem in using it because its low conc.

Main function: T4 (Thyroxine) and T3 carrier. that's why we call it transthyretin