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# Biochemistry

Doctor 2017 | Medicine | JU

Sheet

Slides


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**-We will continue our talk about Globulins:**

## α 1 – antitrypsin (52 kDa)

As the name indicates it's part of the alpha-1 globulins, and its function is to neutralize (work against) trypsin & trypsin like enzymes (elastase).

Also known as antiproteinase was first discovered as an antagonist (neutralizer) for trypsin. Trypsin is a serine protease (hydrolase) that breaks down proteins. It was then found that antitrypsin neutralizes many proteases such as elastase, thus they named it: alpha 1 antiprotease.

It makes 90% of the alpha1- globulin band.

### 1- Elastase

a-Elastase breaks down elastin which Gives elasticity for tissues, elastic tissue can be found in the skin, blood vessels and lungs. In the lungs, elastin is found in the alveolar wall, so it facilitates inhalation and exhalation.

b-Elastase is produced by macrophages (WBC) during inflammation to break down the elastin of microorganism, but it will also affect the elastin in the alveoli walls. And this is when antitrypsin works. Antitrypsin breaks down elastase then the lung tissue is regenerated. So, Antitrypsin **prevents** excessive damage of tissues.

Note: A person will face a problem when there is either:

1) A deficiency of Alpha-1 antitrypsin.

2) Mutated alpha-1 antitrypsin (a copy of the protein that is different than the most common copy of this protein and is pathogenic, it has a slightly different structure, thus affecting its function)

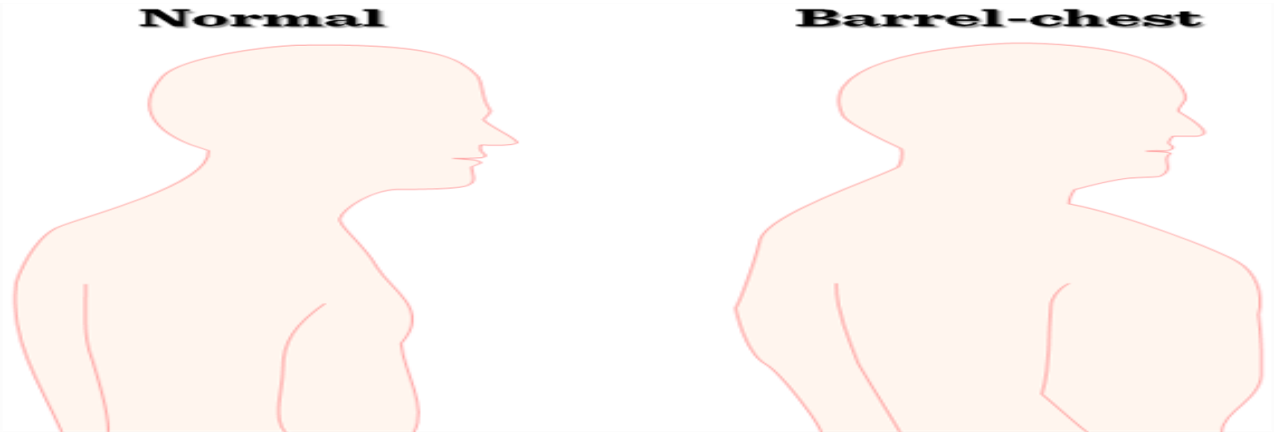
So, if a person has any of the above-mentioned cases, during inflammation, elastase will be released by macrophages and it will work on digesting elastin of the microorganism and elastin of the lungs, but since alpha-1 antitrypsin is not working well or not present in adequate amounts, elastase will continue to digest elastin in the lung causing problems.

Active elastase + $\alpha_1$-AT → Inactive elastase: $\alpha_1$-AT complex → No proteolysis of lung → No tissue damage

Active elastase + ↓ or no $\alpha_1$-AT → Active elastase → Proteolysis of lung → Tissue damage

Note: Elastin is present in the alveoli walls which are present in large amounts in the lungs to increase surface area available for gas exchange and decrease the amount of air present in the lungs, so breaking these walls will decrease the surface area available for gas exchange and increase the amount of air in the lungs, so it would be harder to breathe; less gas exchange because of the decreased surface area, this case is called: **Emphysema.**

-**Emphysema** is characterized by having a barrel chest and difficulty in breathing.




## 2- Genetics and alpha1- antitrypsin

A-This plasma protein has at least 75 polymorphic forms

B-Its alleles are: $Pi^{M}$, $Pi^{S}$ $Pi^{Z}$ ,$Pi^{F}$ .

C-The phenotype **MM** is the most efficient and common one. ZZ and ZS are the weakest forms. ZZ is only **10% as effective** as MM. If one M allele is present, antitrypsin will be effective. So, having 2 copies other than M will cause a problem.

D-The presence of the **ZZ** phenotype can lead to **emphysema**.

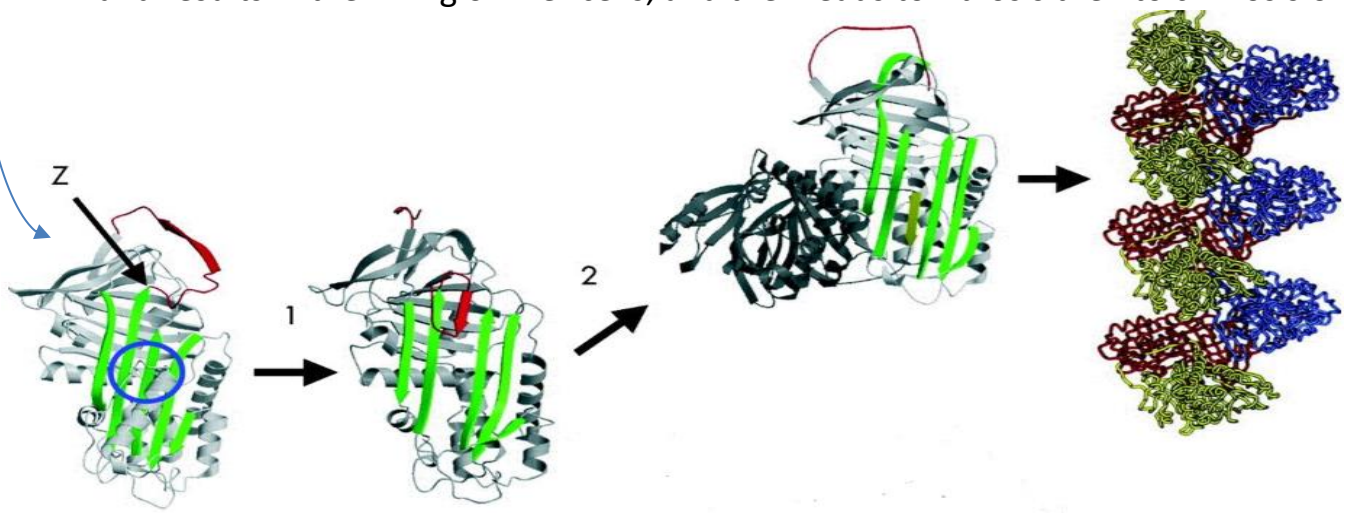
E-**Smoking** is a major cause of emphysema. It causes chronic inflammation, so elastase is always produced by immune cells in the lungs,so, Lung tissue will be broken down. If a person smokes and has a ZZ phenotype, their case will be devastating.

F-**Smoking** can oxidize the **358$^{th}$** amino acid **methionine** to **methionine sulfoxide** in antitrypsin. This residue is on the surface and supposed to bind to the elastase, so smoking will decrease the ability to bind drastically.

-methionine is usually not reactive because its sulfur is internal, but because smoking is harsh it can be oxidized.

G-**Liver**:

A) Alpha-1 antitrypsin is synthesized in the liver.
B) The ZZ phenotype antitrypsin has an **extra loop and beta sheet**. The beta sheet of an antitrypsin protein has high affinity towards the loop of another, So, they will polymerize and form alpha-1 antitrypsin aggregates in the liver which can't leave and results in the killing of liver cells, and then leads to fibrosis then to cirrhosis of the liver.




C) 10% of people with ZZ antitrypsin have cirrhosis.

## C Reactive Protein (CRP)

-When it was first discovered, it was found that it binds with the **C fraction** of the polysaccharide that is present in the cell wall of a type of bacteria called **pneumococci.**

-It is an **acute phase** protein. It is **undetectable** in healthy individuals. But its levels increase in cases of inflammatory diseases (like acute rheumatic fever, bacterial infection, gout), trauma, cancer and tissue damage.

-It helps in the defense against bacteria and foreign object in the body.

-Its level reaches a peak after 48 hours of the incident. Which is used as a monitoring marker. If it is found in high levels there must be a problem that needs to be investigated.

## Bioenergetics

-Bioenergetics describes the transfer and utilization of energy in biologic systems. It makes use of a few basic ideas from the field of thermodynamics, particularly the concept of free energy. In short, bioenergetics predicts if a process is possible, whereas kinetics measures how fast the reaction occurs.

-**Energy** is the capacity to perform work.
The 2 types of energy are:
1-Kinetic energy which deals with movement, rate of the reaction, mechanism of the reaction and deals with enzymes.

2-potential energy (which is more important in our course).

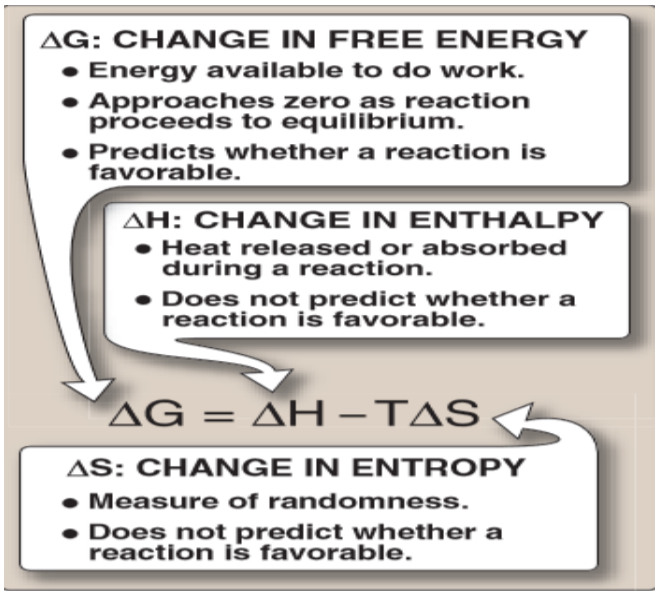
When we study a reaction, we study it from **2 points of view**:

1- How it actually happens (kinetic energy).

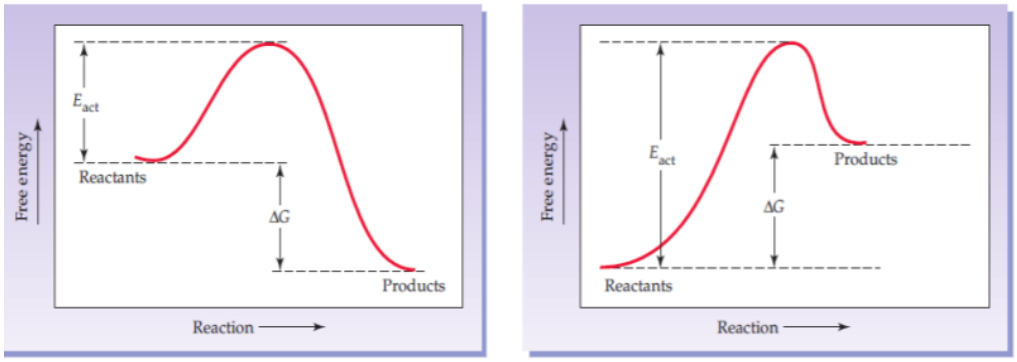
2- Thermodynamically, a prediction science; will the reaction happen or not and will it release energy or does it need energy. (potential energy).

-All chemical reactions occur to reach a more stable state with respect to **total energy**, remember we are talking about energy, not the material we are dealing with, because some reactions will produce a more stable product ( exergonic reactions) and other reactions will produce a less stable product (endergonic reactions), but the total energy in the system in the beginning of the reaction will decrease by the end of the reaction

-**free energy change ΔG**: is the total energy change in a system with respect to its temperature. The sign determines **spontaneity**.



- If ΔG is **negative**, there is a net loss of energy, and the reaction goes spontaneously. The reaction is exergonic.
- If ΔG is **positive**, there is a net gain of energy, and the reaction does not go spontaneously. Energy must be added to the system to make the reaction go from reactants to products. The reaction is said to be endergonic.




(a) An exergonic reaction (b) An endergonic reaction

- **ΔG°** is the **standard** free energy change. It occurs at standard conditions of 1 atm, pH of 7, 25 C, and a concentration of 1M. These conditions can only take place in a **lab**, so it cant predict the direction of a reaction under physiologic conditions.

-The activation energy barrier exists so that reactants can also exist. If it is not there, the reaction will shift all the way to the products side, reactants will cease to exist. The collision of the molecules by themselves are not enough to exceed this energy barrier, there should be heat supplied or the use of an enzyme which will lower the activation energy, other wise the reaction won't happen.

**In metabolism:**

- ΔG determines if the reaction occurs or not (Determines feasibility) not **ΔG°**. Its value is **not affected** by mechanisms or steps. For example, combustion of **1 mole** of glucose in a lab gives out 680 kcal/mol. And breaking it down to CO2 in metabolism through glycolysis and citric acid cycle will also have the same value.

-Breaking substances down **gives out** energy.

Building substances **requires** energy.

-**Potential energy** is the energy stored in bonds which is free energy, so the change in free energy is the difference in bond energy between products and reactants.

-As concentration increases, bond energy increases as there will be more molecules present. Controlling the concentration affects the direction of the reaction; increasing [reactants], increases the rate of the forward reaction.

-The Concentration of reactants and products affects the value ΔG which can be shown in the following equation:

For a reaction $A + B \leftrightarrow C + D$

$$\Delta G = \Delta G^{o\prime} + RT \ln \left( \frac{[C]\,[D]}{[A]\,[B]} \right)$$

Where T: temperature (K)

R: gas constant

Keep this in mind:

Ln(x)=0, x=1

Ln(x)=+ve, x>1

Ln(x)=-ve, x<1

If the product is constantly being taken from the system, like breaking pyruvate down by enzymes in the case of metabolism, the products/reactants ratio will be **less than 1**, so ln(products/reactants) is **negative.**

-By changing concentrations, you can have a Negative ΔG for a reaction that originally has a positive **ΔG°.** What this means is that a reaction that is endergonic under standard conditions could be exergonic under physiologic conditions.

-Remember that at equilibrium:

1-The rate of the forward and backward reactions are equal. (equilibrium is dynamic not static)

2- The concentration of products and reactants are not necessarily equal.

3- The concentrations of both products and reactants are constant.

*Exergonic reaction>>>-ve ΔG>>>favorable(feasible) in the forward direction>>> releases energy>>>unfavorable in the backwards direction

*Endergonic reaction>>> +ve ΔG>>>Unfavorable(infeasible) in the forward direction>>>needs energy>>> favorable in the backwards direction