Doctor 022

Biochemistry

Sheet no. 14

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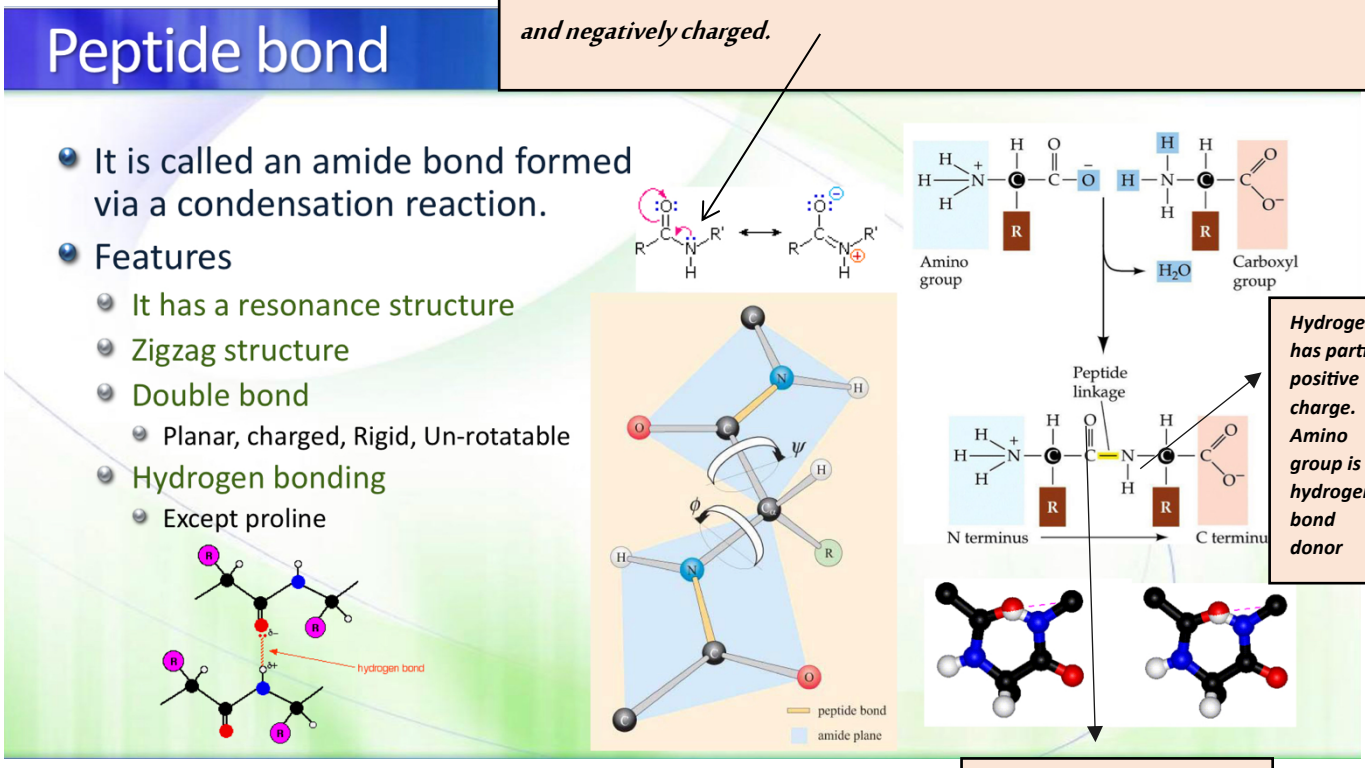
Peptides

Peptide bond is considered to be formed via a condensation reaction because water is produced. This peptide 'amide' bond is formed by the combination of the carboxyl group of the *end of the 1st amino acid* with the amino group of the *beginning of the 2nd amino acid*. In biochemistry, it's more frequent to call it 'peptide bond' because a peptide is the final product.

Ex. A peptide composed of 2 amino acids is called "Dipeptide".

The unshared pair of electrons on the Nitrogen will be shared between the Carbon and the nitrogen, forming a Pi bond and Nitrogen will be positively charged.Also the pair of electrons in the bond formed between Carbon and Oxygen will move and thus oxygen will have another pair of unshared electrons and negatively charged.



Hydrogen has partial positive charge. Amino group is a hydrogen bond donor

Oxygen has partial negative charge. Carbonyl group is a hydrogen bond acceptor.

Let's talk about the *features*:

1. **The bond's shape changes due to having resonances.**
2. **It can be charged (with real charges) due to movement of electrons.**

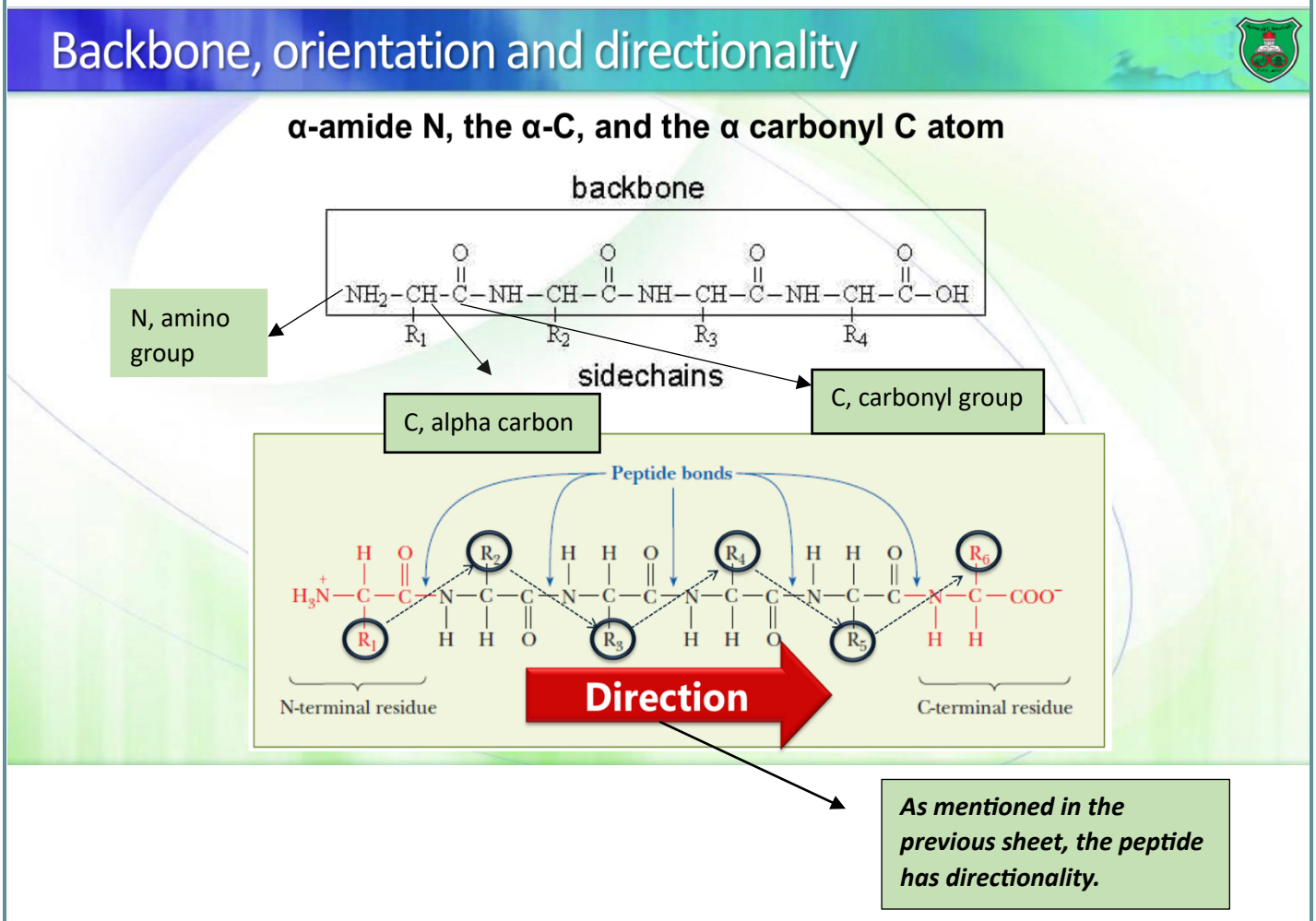
3. **Having a double bond makes this covalent bond stronger, shorter, more stable and flexible (Fixed, strong and doesn't rotate) and this has an importance regarding the protein's structure. Yet, protein has kinks and curves, this is because the bonds (around the alpha carbon) within the amino acid move and rotate , but the peptide bond *doesn't move at all*. Consequently, the peptide bond is *flat.***

4-The components (atoms) that make the peptide bond can participate in hydrogen bonding and that has an impact on the stability of the protein's structure. Remember that the non-covalent interactions determine stability and shape of the protein's structure ex: secondary structure . However, peptide bond is presented but eventually the amino acid is going to rotate and adopt the appropriate position where it doesn't repulse with the surroundings which results in

destruction of the protein (also possess the least amount of energy to maintain stability).
***Consider the notes on the figure**

5. The 4th note applies to all of the amino acids except for one, Proline. Proline is the only cyclic amino acid which has a secondary nitrogen (already bonded to 2 carbons: the alpha carbon, and the carbon in the R chain). When nitrogen participates in the peptide bond, that's the 3rd bond formed with a carbon, which makes nitrogen already bonded with 3 covalent bonds. So it doesn't have any remaining bonds with hydrogen, which can't be a hydrogen bond donor! To conclude, Proline is the only amino acid that's when involved in a peptide bond loses the hydrogen (that Nitrogen was previously bounded to) and Nitrogen loses its ability to be a hydrogen bond donor.
****Note that the carbonyl group can still be a hydrogen bond acceptor, but Nitrogen(in the amino group) cannot be a hydrogen bond donor.**

Now let's talk about peptides especially when we have multiple amino acids that are stretched and involved in peptide bonds..



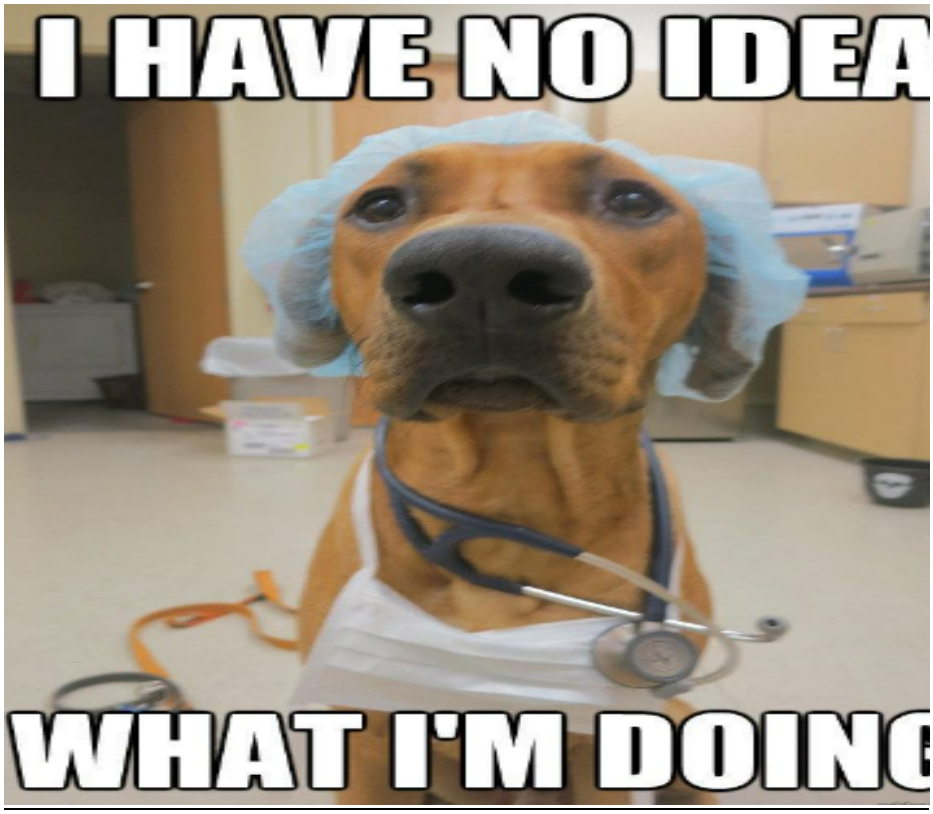
Let's define some crucial definitions:-

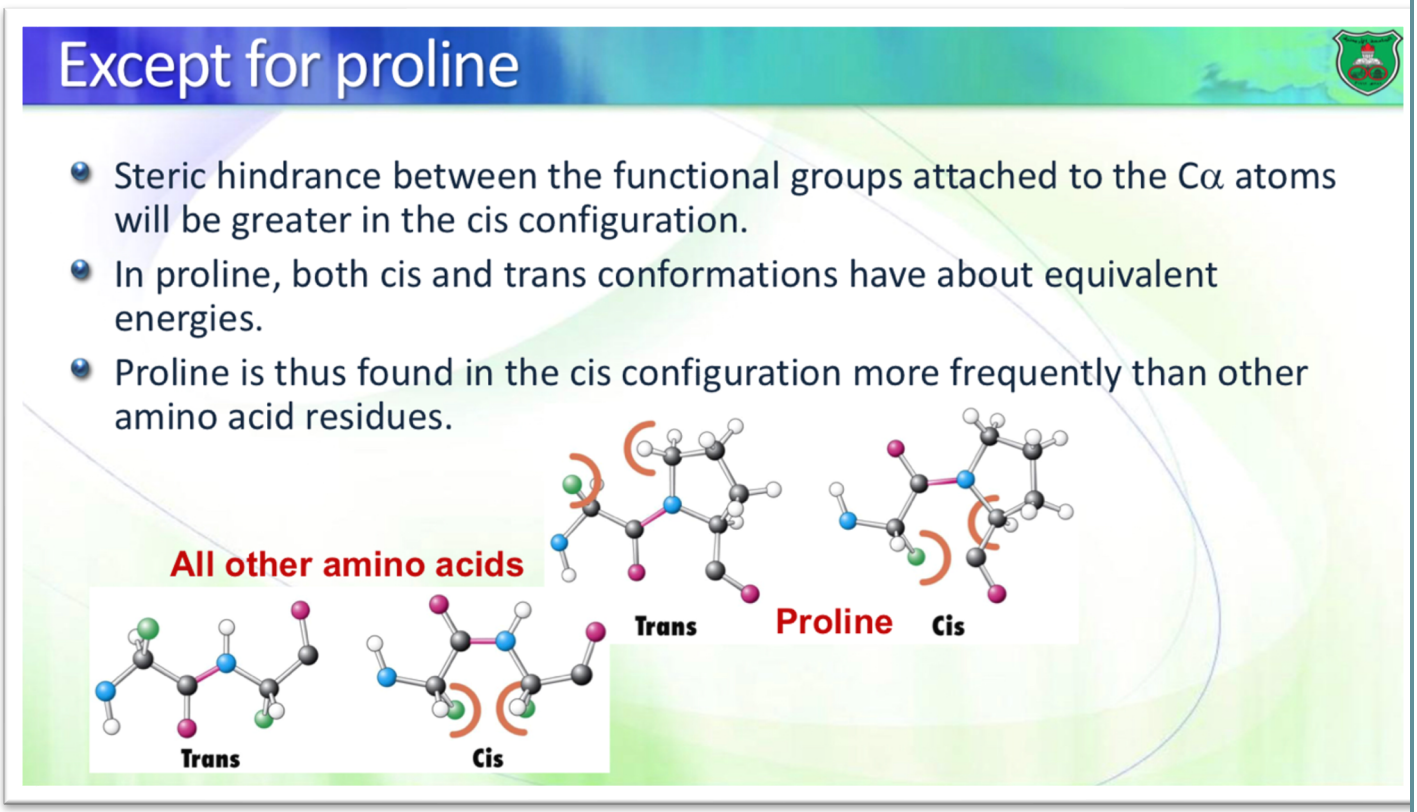
Backbone: **"العمود الفقري" Consists of (amino group, alpha carbon, carbonyl group); Symbolized as (N,C,C).**

So the backbone is the basis which the 'R groups' are bounded to as side chains.

Side chains : **the 'R groups' which extend out of the backbone. Note that the 'R groups' have to be in the trans configuration (Up,down. Up,down. Up,down), why?!! To minimize the repulsion between the R groups.**

Directionality: **the peptide has a specific direction, so when we read the order of the amino acids we have to start from the *amino group.* So the 1st amino acid starts with an amino group "N-terminus" and the last amino acid ends with a carboxyl group "C-terminus". Also, when an amino acid is added to the peptide, it is added to the carboxyl group "C-terminus".**





So, as we said, the R groups exhibit the trans configuration, except for the usual *troublemaker* : Proline.

Proline is rigid and cyclic. whether it's in the trans orientation or the cis orientation, it will be unfigurable and will make repulsion. As a result, in any random peptide with no Proline, 90-95% of the groups will be in the trans configuration. But when Proline exists, there's no preference of a specific orientation and 50% of the groups will exhibit the cis orientation and the other 50% will exhibit the trans orientation.

Examples of functional and exceptional Peptides:

as we know In a peptide chain, the amino group of one amino acid reacts with the carboxyl group of another amino acid, forming a peptide bond. This reaction results in the formation of a peptide bond and the growth of the peptide chain.

The general rule is that the peptide chain starts with an amino group and ends with a carboxyl group. However, there are some exceptions, let's get to know them!

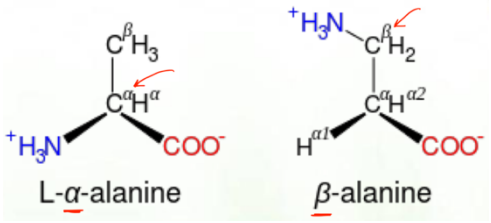
Carnosine (ß-alanyl-L-histidine)

*A dipeptide of β-alanine and histidine.

"ß-alanyl-L-histidine" it is composed of two amino acids, beta-alanine and histidine, that are linked together by a peptide bond.

*The amino group is bonded to the β-carbon of alanine

The β in β-alanine refers to the position of the amino group on the β-carbon, which is located at the second carbon in the amino acid. Therefore, we call it β-alanine because the amino group is linked to the β-carbon, not the α-carbon as is typical.



***Remember: α-carbon, which is located on the first carbon in the amino acid.**

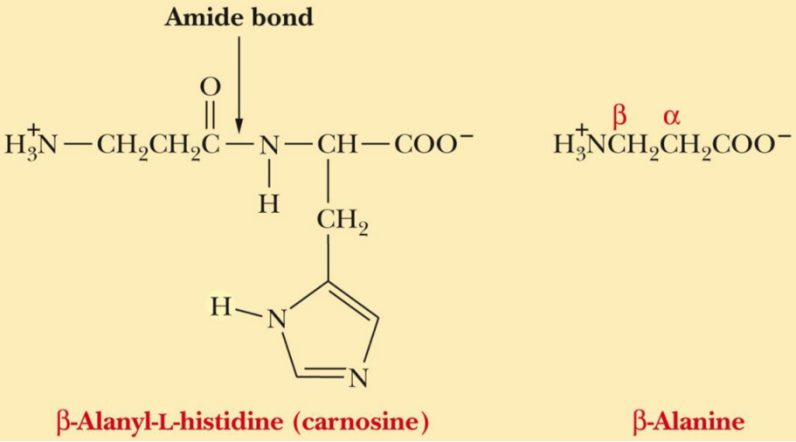
*It is highly concentrated in muscle and brain tissues

-Protection of cells from ROS (radical oxygen species) and peroxides

A radical is a molecule or atom that has one or more unpaired electrons in its outermost shell, which makes it highly reactive, because of their high reactivity, radicals can cause damage to cells and tissues by oxidizing DNA, proteins and lipids which can lead to a variety of diseases and conditions.

ß-Alanyl-L-histidine is classified as antioxidants. Antioxidants, can help prevent oxidative damage by scavenging radicals and neutralizing their reactivity. So it can help protect cells and tissues from the harmful effect of the radicals and peroxides.

-Contraction of muscle



***Notice that histidine looks like the base for this molecule, and alanine looks like a branch from the histidine. Because of that, we named it alanyl not alanine**.

in another words: histidine molecule carrying the alanine molecule with it. you can go back to systemic names of disaccharides to understand deeply.

Glutathione:

(γ-glutamyl-L-cysteinyl glycine)

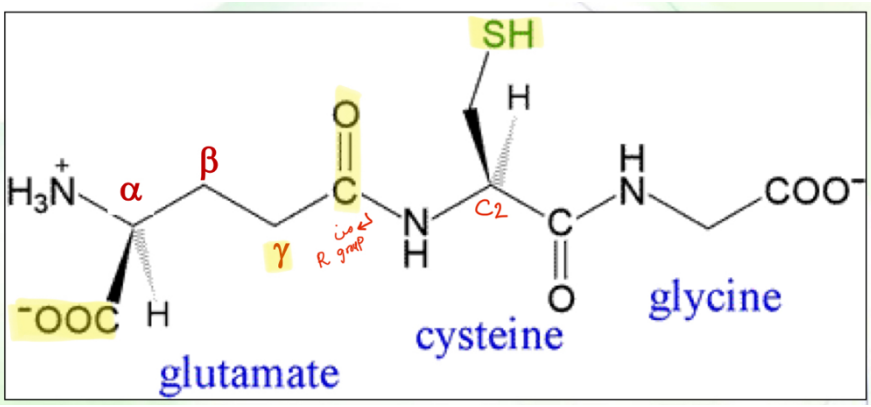
Glutathione is a tripeptide that consists of the three amino acids glutamate, cysteine, and glycine.

When a peptide bond is formed in γ-glutamyl-L-cysteinylglycine, it forms between the carboxyl group of the R chain located on the gamma carbon (not the carboxyl group in the backbone) with the amino group of the next amino acid.

Cysteine contains a sulfhydryl group (-SH).

Thiols (The sulfhydryl group is what defines a thiol) in general are indeed very reactive. The reactivity of thiols is due to the presence of the sulfhydryl group.

Glutathione is important because it contains a sulfur-hydrogen bond that is easily oxidized. When there are radicals or reactive oxygen species are present, glutathione can donate electrons to neutralize them. This is a crucial antioxidant function that helps to protect cells from damage caused by radicals.



Function of glutathione

Now how does the oxidation process occur?

***It scavenges oxidizing agents by reacting with them.**
***Two molecules of the reduced glutathione molecules form the oxidized form of glutathione by forming a disulfide bond between the -SH groups of the two cysteine residues.**
Then some enzymes are responsible for reducing it back to its active form (the reduced form). This allows the glutathione to be used again to donate electrons to radicals or reactive oxygen species that enter the body.

Enkephalins

***Two pentapeptides (consists of 5 amino acids) found in the brain known as enkephalins, and function as analgesics (pain relievers). Enkephalins work like endorphins. Enkephalins are peptides that are naturally produced by the body in response to pain or stress, and they help to reduce the feeling of pain.**
-They differ only in their C-terminal amino acids. (There are two types of enkephalins: one that ends in "met" and the other that ends in "leu", which means that the difference is in the last amino acid)

-Met-enkephalin: Tyr-Gly-Gly-Phe-Met
-Leu-enkephalin: Tyr-Gly-Gly-Phe-Leu
-The aromatic side chains of tyrosine and phenylalanine play a role in a their activities. The specific arrangement of atoms in the aromatic side chains of tyrosine and phenylalanine is essential for the biological activities of enkephalins. These two amino acids are the most important components of enkephalin's function.
***There are similarities between the three-dimensional structures of opiates, such as morphine, and enkephalins.**
The structure of morphine is very similar to that of enkephalins, which allows it to interact with the same receptors in the body. This interaction can help to reduce the sensation of pain. Because of its pain-relieving and sedative effects, morphine is often used after surgeries. However, it is important to note that morphine can be highly addictive and can have other negative side effects, so it should only be used under the guidance of a medical professional.

Nice video about opiates: https://youtu.be/scvEyLXINpQ

Oxytocin and vasopressin

Hormones with cyclic structures due to S-S link between Cys. Both oxytocin and vasopressin are peptide hormones that contain two cysteine residues. These residues are able to form a disulfide bond, which causes the molecule to fold into a cyclic structure. This cyclic structure is important for the hormones' biological activity.

Both have amide group at the C-terminus instead of a carboxyl group. This modification helps to increase the stability of the hormones by making them more resistant to enzymatic degradation in the body.

Both contain nine residues, but: (The doctor said that we should not memorize all of the details about the chemical structure of these hormones)
differences between them in amino acid number 3&8:
Oxytocin has isoleucine and leucine.

Vasopressin has phenylalanine and arginine .

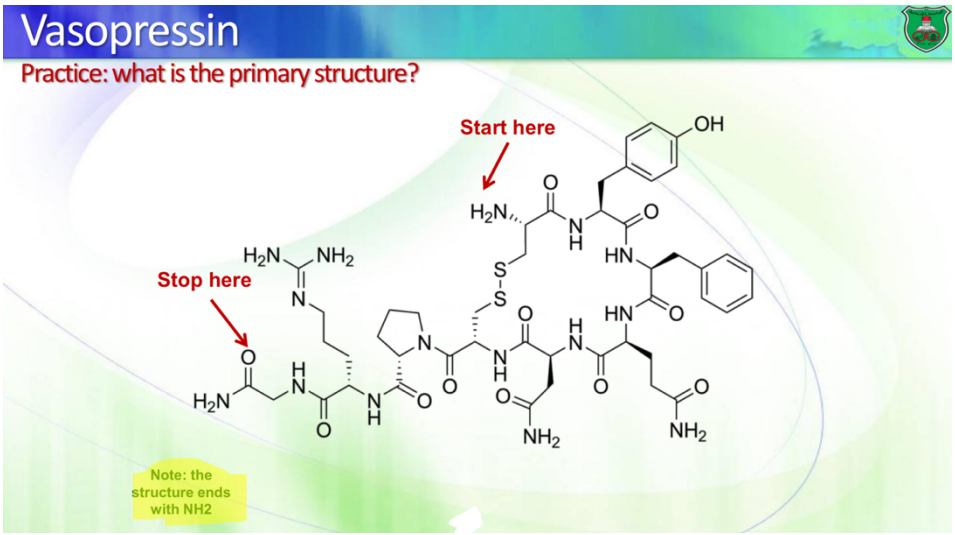
Oxytocin regulates contraction of uterine muscle (labor contraction).

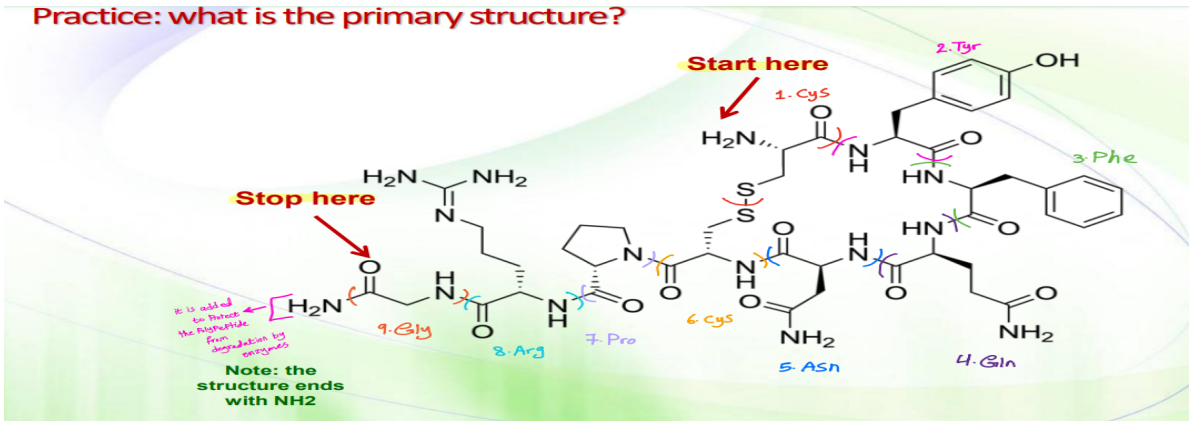
Smooth muscles يا محترمين

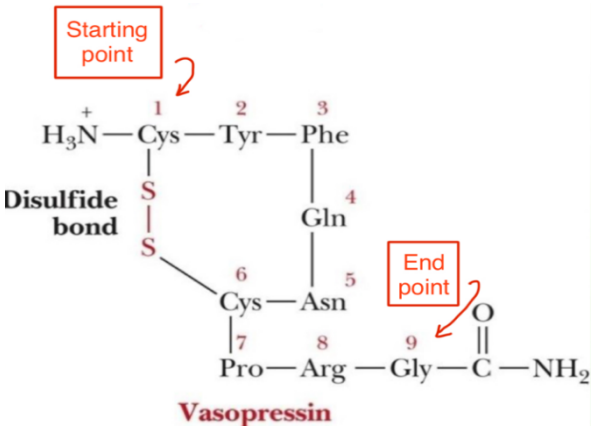
Oxytocin is a hormone that is plays an important role in the female reproductive system, particularly during childbirth and breastfeeding. During labor and delivery, oxytocin is released in large amounts, which helps to stimulate contractions and facilitate the birthing process. After delivery, oxytocin continues to be released

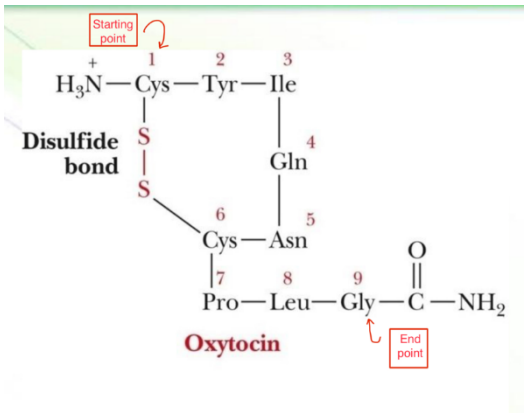
during breastfeeding that doesn't mean that males and females at normal don't have oxytocin.

Vasopressin is another hormone that is plays an important role in contraction of smooth muscle, increases water retention, and increases blood pressure as a result.

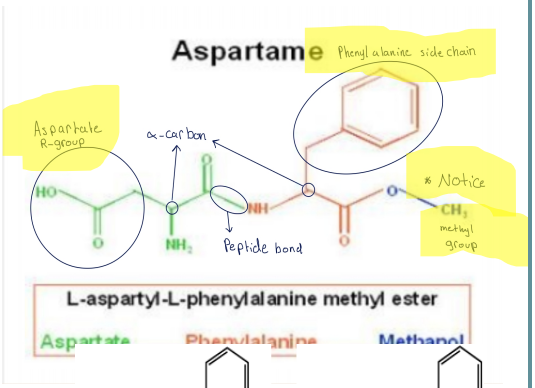








Aspartame



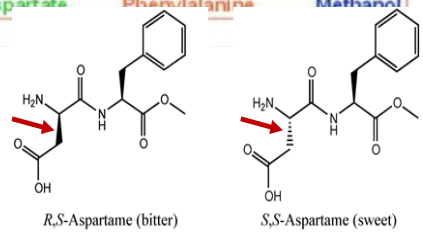
L-ASPARTYL-L-phenylalanine(methyl ester)

-An artificial sweetener not a sugar

-it is a dipeptide that is 200 times sweeter than sugar.

-structure: it is aspartate followed by a phenylalanine

Notice: that the carboxyl group of the second amino acid is attached with a methyl group ; increases the stability of the molecule.

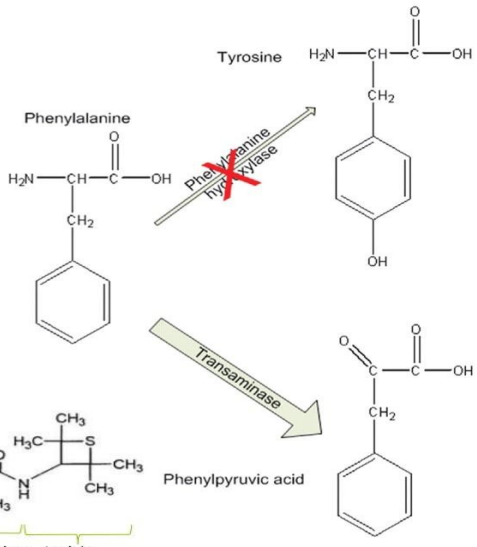


-If a D-amino acid is substituted for either amino acid or for both of them, the resulting derivative is bitter rather than sweet.

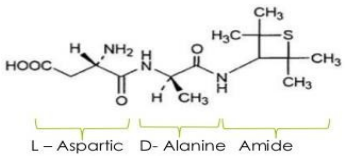
Aspartame and cancer :it may cause cancer

Phenylketonuria (PKU)

- people cannot metabolise phenylalanine, because of the deficiency of phenylalanine hydroxylase that transforms Phenylalanine to tyrosine. But when it is defected the phenylalanine will transform to phenyl pyruvic acid that will accumulate causing cell death, it is toxic when it is in high amounts.



- PKU is a hereditary "<u>inborn</u> error of metabolism" caused by defective enzyme, phenylalanine hydroxylase.

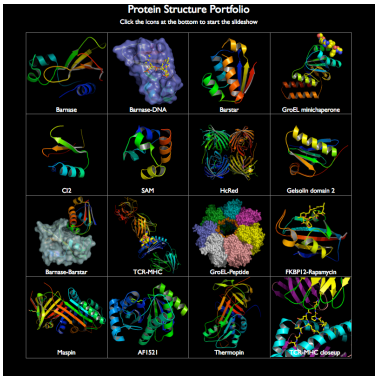


- It causes accumulation of phenylpyruvate in CNS, which causes mental retardation.
- Adults that suffer from this disorder, the Sources of phenylalanine such as <u>aspartame must be limited,</u> as well food that contains proteins should be in small amounts .
- A substitute for aspartame, known as <u>alitame</u>, contains alanine rather than phenylalanine.

- https://youtu.be/HYg0Id-C0uQ **another nice video about PKU**

PROTEIN STRUCTURE

Overview of proteins



*Recall the difference between the polypeptide and protein ,a polypeptide doesn't have a defined structure while protein does.

- Proteins have different structures, and some have repeating inner structures, other do not.
- How many structures may the protein have ?! protein may have *gazillion(*unlimited number*)* possibilities of structures, but a few would be active ; because the protein takes a form which it needs the least energy to keep it stable .
  TO SUM UP: theoretically the protein can have many structures; but realistically it has one structure which is the most stable one, it is not a random formation.
- These active structures are known as native conformations (the 3-dimensioanl structure of a properly folded and functional protein).
  The cell get rid of the not probable folded functional protein

If we know the structure, we will know the function and how it is related to diseases to make drugs that targets that protein,

Since sixties, scientists had tried to find a way to predict the protein structure, In 2020, AI programs have been published, Successfully, they're able to predict proteins in high success rate using artificial intelligence.

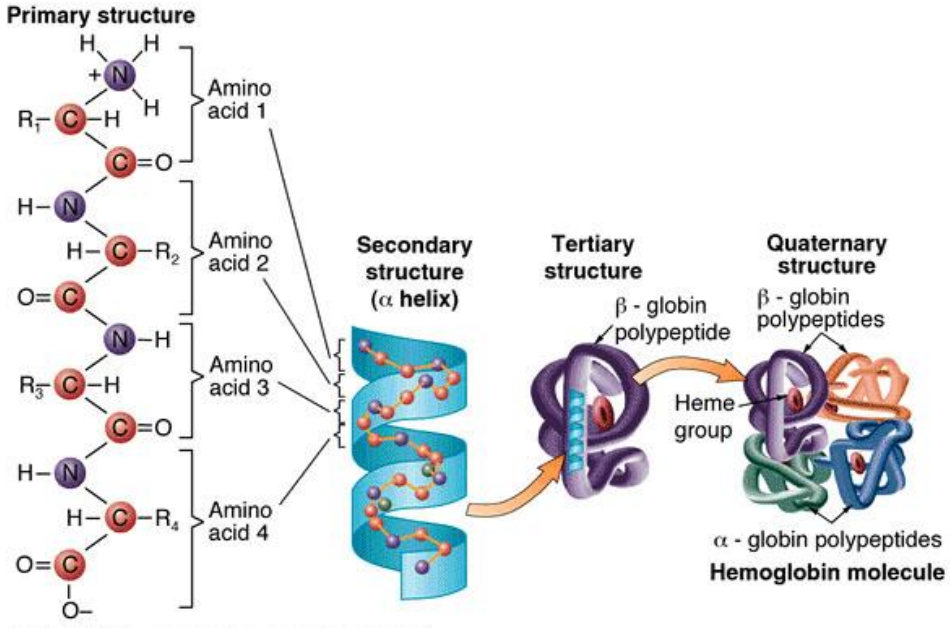
😈 بالمناسبة هاد الشيت فخم الانو الادمن اشتغلو عليه حد عندو مانع

Levels of protein structure

depending on the complexity

- *Primary structure*: the sequence of amino acid residues, starting from the N-terminus to the C-terminus
- *Secondary structure*: the localized organization of parts of a polypeptide chain, on a specific location on the protein, amino acids would make a distinct structure.

- *Tertiary structure*: the three-dimensional structure and/or arrangement of all the amino acids residues of a polypeptide chain, how the secondary structures are organized in 3D structure (a structure in the front or in the back, up or down relating to the other secondary structures), it is a 3D structure of one single polypeptide
- Some proteins are made of multiple polypeptides crosslinked (connected) with each other. These are known as multimeric proteins. *Quaternary structure* describes the number and relative positions of the subunits in a multimeric protein.



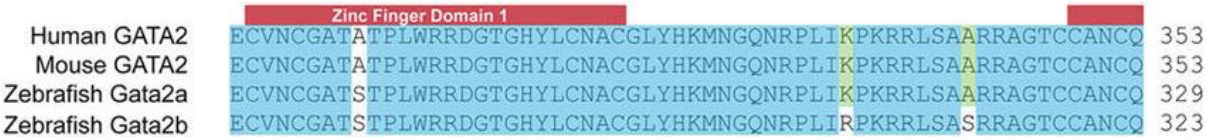
Sequence of amino acids→ organised together to make a helix structure it is repeated in different locations → they gathered together to make 3D structure of one single polypeptide→ It connected with other polypeptides to make the quaternary structure.
It looks like neighbor the brick is primary and the door is secondary, and the building is tertiary, guess what will be quaternary?

Primary structure

- The order in which the amino acids are covalently linked together.
  - Example: Leu—Gly—Thr—Val—Arg—Asp—His
- The primary structure of a protein determines the other levels of structure.

- Proteins that differ somewhat in primary structure and properties from tissue to tissue, but that retain essentially the same function, are called tissue-specific isoforms or isozymes.
    - Example: Hemoglobin, there are types of hemoglobin proteins, they have a similar primary structure with slightly differences that

    is important for the function of each one of them
- Check the figure above ; same protein in different organisms, blue highlight represents the same sequence, the white one represents the differences.
  The proteins that has the similar function and structure in different organisms has mostly the same primary structure
  The slightly differences make the organisms different .
  That's why mice are used in our studies because we have the same mechanisms, proteins and so on.



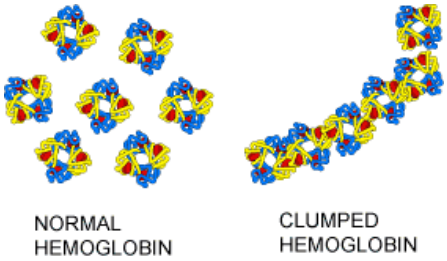
Sickle cell haemoglobin (Hbs) فقر الدم المنجلي

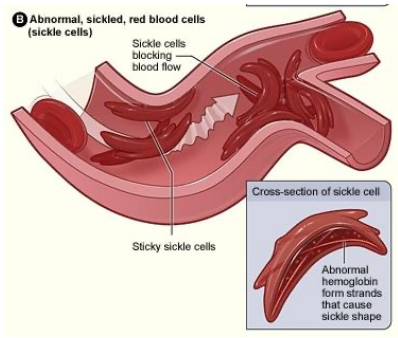
Here we will understand the importance of primary structure

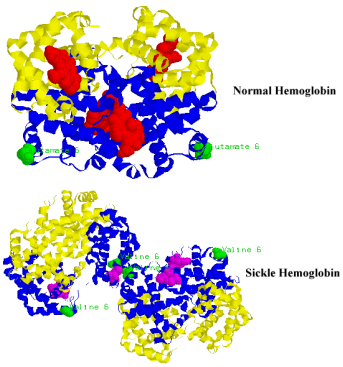
- ✓ A single amino acid substitution can give rise to a malfunctioning protein, as is the case with sickle-cell anemia.
- ✓ It is caused by a change of amino acids in the 6th position of β globin (Glu to Val). So, the 1° structure changed then 2° then the 3° then the quaternary structure changed, all of that happens because a change in a nucleotide in the nucleic acid that changed the amino acid

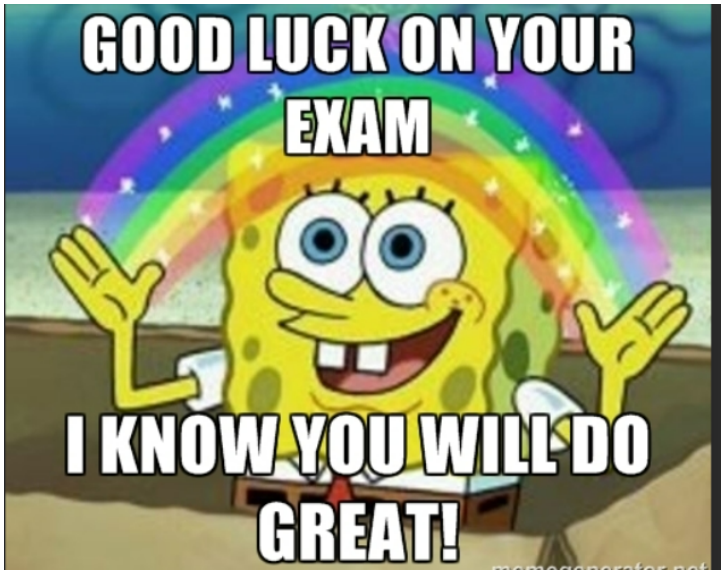
The mutation results in:
1) arrays of aggregates of hemoglobin molecules, 2) deformation of the red blood cell, it is sickled, looks like a crescent, cant Carrie oxygen efficiently.

3) clotting in blood vessels and tissues









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M.Z.R

Test yourself:

1) Which of the following statements is true about enkephalins?

A) Enkephalins are hexapeptides found in the brain, involved in muscle contraction.

B) Met-enkephalin and Leu-enkephalin differ in their N-terminal amino acids.

C) The presence of aromatic side chains in tyrosine and phenylalanine contributes to the analgesic (pain-relieving) activities of enkephalins.

D) Enkephalins have a three-dimensional structure similar to that of proteins.

2) Which of the following hormones is characterized by a cyclic structure due to an S-S link between Cysteine residues and regulates labor contraction in the uterine muscle?

A) Oxytocin

B) Vasopressin

C) Insulin

D) Thyroxine

3) Which hormone contains nine residues, including phenylalanine and arginine, and is responsible for regulating smooth muscle contraction, increasing water retention, and elevating blood pressure?

A) Oxytocin

B) Vasopressin

C) Growth hormone

4) What is the composition of carnosine, a dipeptide found in high concentrations in muscle and brain tissues, known for protecting cells from ROS (radical oxygen species) and peroxides?

A) Glycine and leucine

B) Glutamine and arginine

C) β-alanine and histidine

D) Serine and lysine

5)Carnosine is highly concentrated in which tissues of the body and is associated with functions like protecting cells from ROS, peroxides, and playing a role in muscle contraction?

A) Liver and kidney tissues

B) Heart and lung tissues

C) Muscle and brain tissues

D) Skin and connectiv

6) Among the following amino acids, which one is found more frequently in the cis configuration due to the equivalent energies of both cis and trans conformations and the greater steric hindrance between functional groups attached to the Cα atoms in the cis configuration?

A) Glycine

B) Aspartic Acid

C) Proline

D) Valine