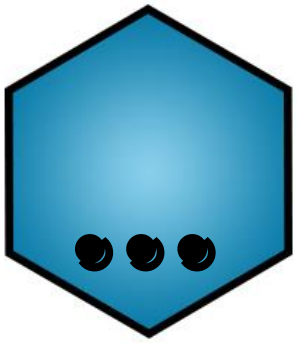

Faculty of medicine – JU2018

◉ Sheet ○ Slides

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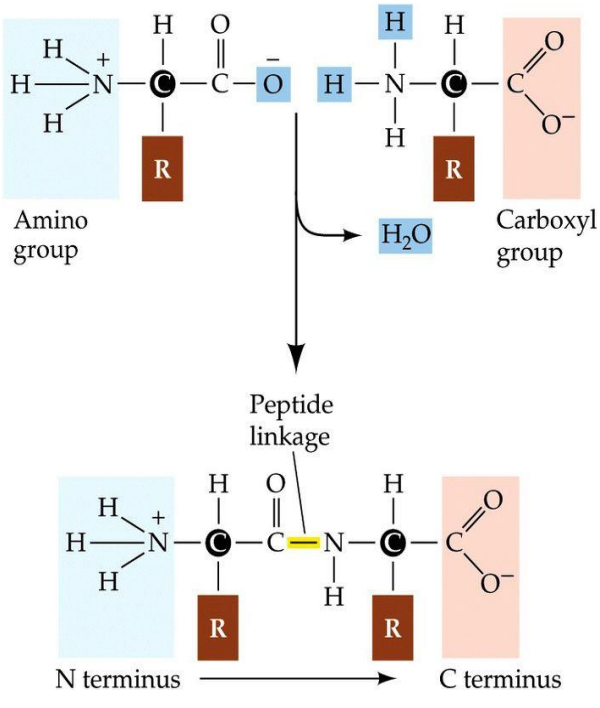
Definitions & concepts to be familiar with:

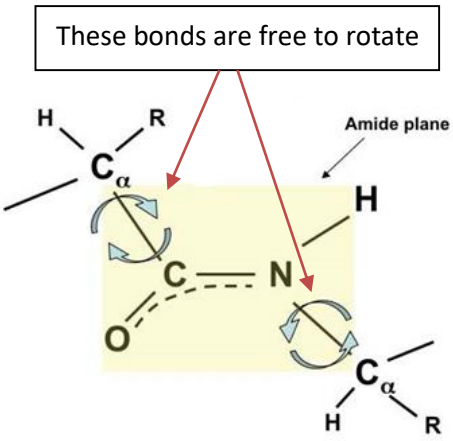
- Residue: Monomers that are linked to each other forming a larger polymer. In other words, it is the constituents that exist in the chain of a larger molecule. (e.g. glucose in glycogen & starch, amino acids in hemoglobin)
  - Protein residue: Each amino acid in a polypeptide.
- Dipeptide: 2 amino acids linked together by a peptide bond.
  - Same concept for Tripeptides, Tetrapeptides et cetera
- Oligopeptide (or just a peptide): A short stretch of about 2-30 amino acids.
- Polypeptide: A longer peptide but with no particular shape. Just a long chain of amino acids.
- Protein: A polypeptide chain that has a distinct & organized 3D shape and structure.

The average molecular weight of an amino acid residue (amino acid in a polypeptide or a protein) is about 110.
Therefore, the MW of most proteins are between 5,500 & 220,000.
Meaning that most proteins have between 50 to 2000 amino acids. (answer to slide question)
We prefer using Daltons as a measure of weight.
A 10,000 MW protein has a mass of 10,000 Daltons or 10 kDa.
NOTE: these numbers are estimates and not the exact values.

- A peptide bond (Amide bond chemically), is when a reaction occurs between the carboxylic group (COO^-) of one amino acid, and the amino group (NH_3^+) of another amino acid. Forming peptides.
- The peptide bond is formed via a condensation (dehydration) reaction. Where a water molecule (H_2O) is released as a by-product.



Properties & features of peptide bonds:



- The peptide bond exists in resonance. Meaning that it has double bond characteristics.
  - ➢ It exists in a zigzag orientation (just like a trans fatty acid)
  - ➢ It is planar (flat)
  - ➢ It is rigid (strong)
  - ➢ The peptide bond does not rotate.
    - o However, other bonds within the amino acid can freely rotate. Look at the animation in slide 6 for better understanding.
- It can hydrogen bond with each other.
  - ➢ The oxygen linked to the carbon of the carboxylic group is partially negative. Can accept a hydrogen bond.
  - ➢ The Hydrogen linked to the nitrogen of the amine group is partially positive. Can donate a hydrogen bond.
    - ▪ **Exception is proline. (It has a secondary nitrogen)**

Backbone of a peptide includes:

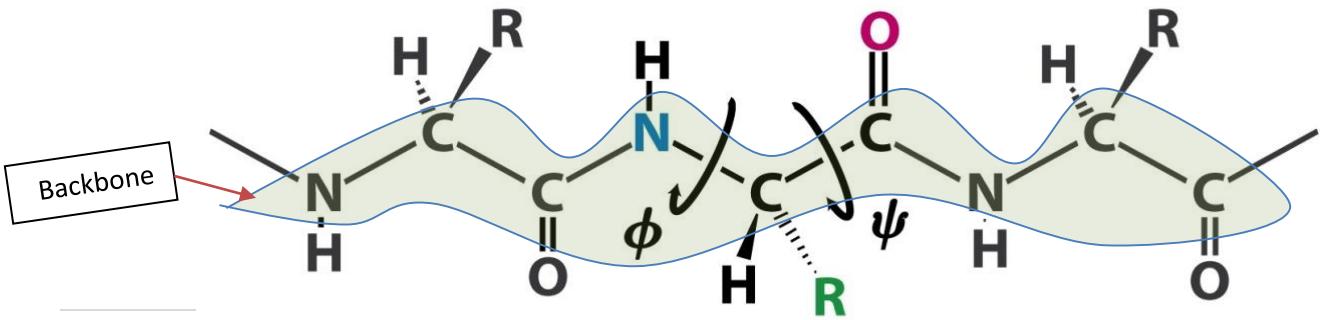
i. The amine group
ii. The α carbon
iii. The carbonyl carbon

The orientation of the peptide is determined by:

The R groups of the constituent amino acids.
They are in the trans orientation. (One R group is directed upwards followed by one directed downwards and so forth).

Why are the R groups in the trans orientation?

- ➢ In order to reduce steric tension between the R groups. It is energetically favoured to have them in this orientation.

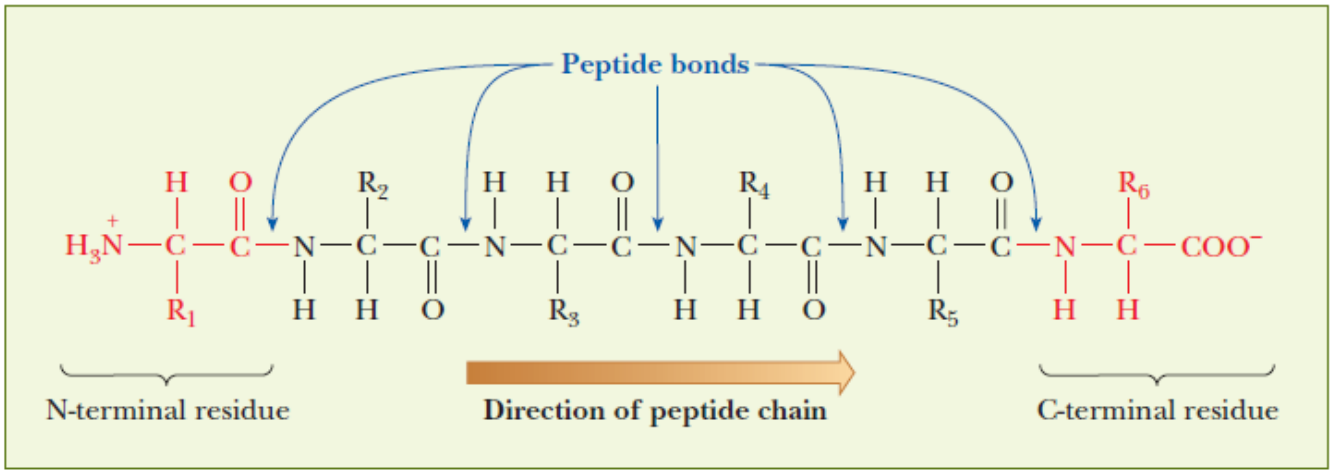


Directionality & polarity

Just like DNA where we have 5’ end and 3’ end, proteins also have a direction in order to be read.

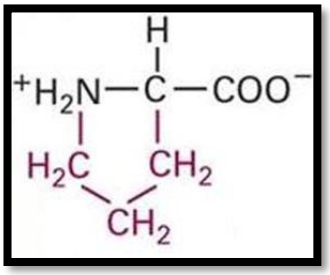
Polarity means that the peptide has a positively charged amino group in the beginning of the peptide. And a negatively charged carboxylic group at the end of the peptide.

In order to read a peptide sequence correctly, we start at the positively charged amino group (the amino terminus or the N-terminus). And we end at the negatively charged carboxylic group (the carboxylic terminus or the C-terminus).



Proline deviation

- Due to the special structure of proline, the R groups can exist in either the cis or the trans orientation because both conformations have nearly equivalent energies.
  - This is because in both orientations there is repulsion.
- Proline exists more in the cis conformation compared to other amino acids.



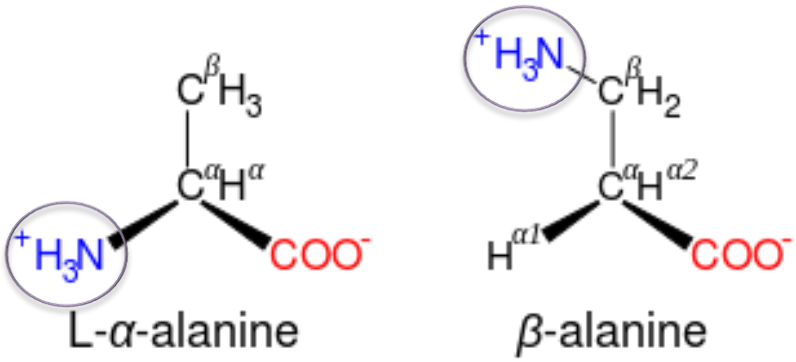
Structure of proline

“Fate is like a strange, unpopular restaurant filled with odd little waiters who bring you things you never asked for and don't always like”.

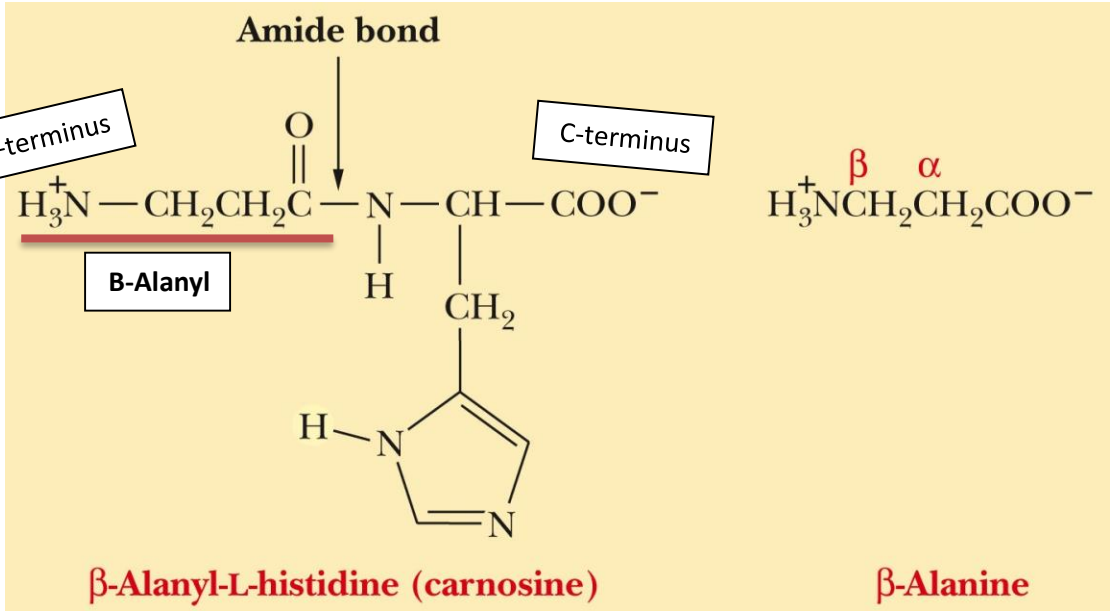
Examples on functional peptides:

I. **Carnosine (β-alanyl-L-histidine)**

- Carnosine is a dipeptide made from β alanine and L histidine.
- The difference between β-alanine and α-alanine is that in β-alanine the amino group is bonded to the β-carbon of alanine.

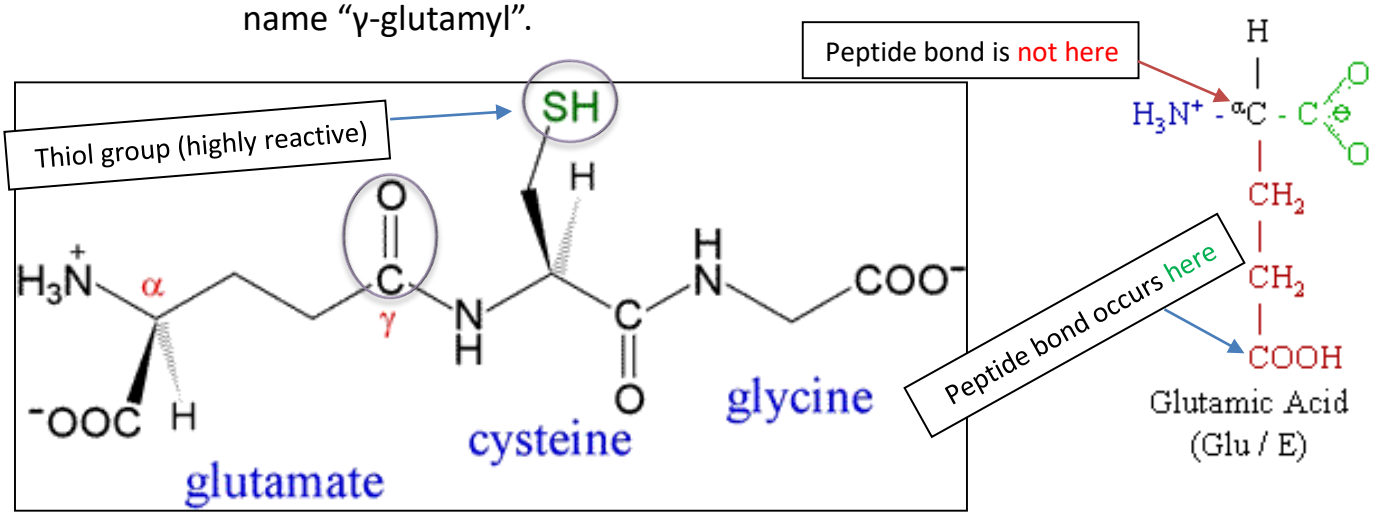


- It is highly concentrated in brain and muscle tissues.
- Functions of carnosine:
  a) It protects cells from reactive (radical) oxygen species & peroxides
  b) Contraction of the muscle



II. **Glutathione (γ-glutamyl-L-cysteinylglycine)**

- It is made up of 3 amino acids (tripeptide)
  a) Glutamic acid (Hence, the prefix "gluta")
  b) Cysteine (Hence, the prefix "-thio-" since cysteine contains a thiol group)
  c) Glycine (Hence, the prefix "-ne")
- The peptide bond between the cysteine and the glutamate is formed by the carboxylic group linked to the γ-carbon and NOT the α-carbon. Hence, the name "γ-glutamyl".



- Functions of glutathione:
  a) It is an antioxidant. Meaning that it removes *oxidizing agents.* And it does so by oxidizing itself. (It reduces other molecules).

- The previous reaction is all enzymatic.

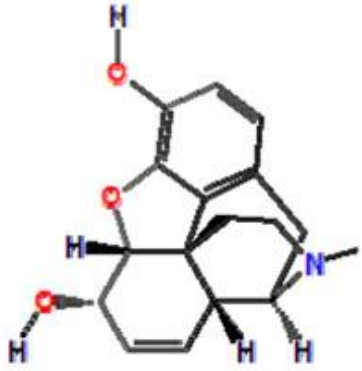
III. **Enkephalins**

- They are pentapeptides (5 amino acids) found in the brain. And they function as analgesics (pain relievers).
- The two enkephalins are:

They only differ with the C-terminus amino acid

a) Met-Enkephalins N terminus-Tyr-Gly-Gly-Phe-**Met**-C terminus
b) Leu-Enkephalins N terminus-Tyr-Gly-Gly-Phe-**Leu**-C terminus

- The aromatic side chain of tyrosine and phenylalanine play a role in the function of enkephalins.
- The structure of **morphine** and **enkephalins** are somewhat similar. And therefore they have similar functions.



Morphine

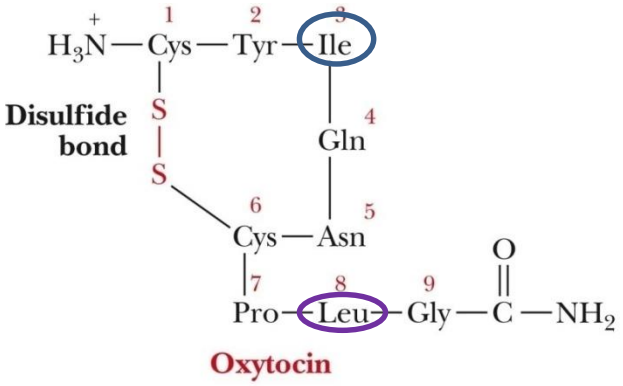
Enkephalins

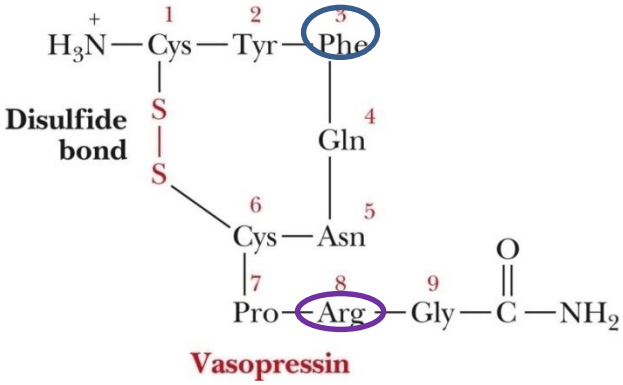
Drugs do not have to look exactly like the normal physiological molecule.
As long as the functional group is the same, as in morphine, the drug will mimic the molecule function.

IV. **Oxytocin & vasopressin**

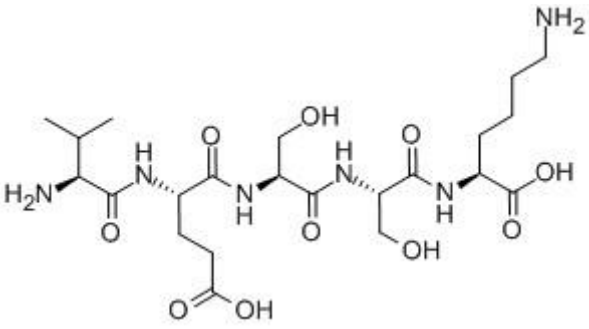
- Oxytocin function is to regulate contraction of the uterine muscle (during labor)
- Vasopressin function is contraction of smooth muscles, increase water retention, and increase blood pressure.
- Both oxytocin & vasopressin contain 9 amino acids, but:
  - Oxytocin contains isoleucine & leucine.
  - Vasopressin contains phenylalanine & arginine.

- Little differences have huge effects on the function of a peptide.





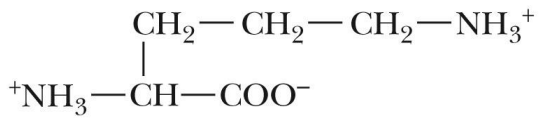
Exam question: What is the amino acid sequence of this peptide?



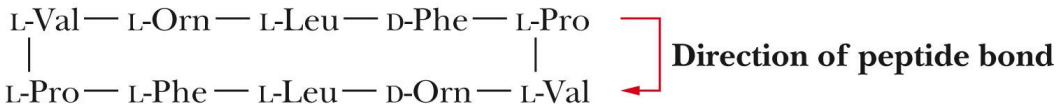
ANS: Val-Glu-Ser-Ser-Lys

V. **Gramicidin S & Tyrocidine A**

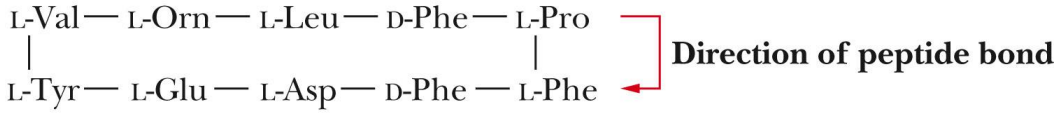
- They are bacterial peptides (bacterium bacillus brevis)
- They are cyclic decapeptide (10 amino acids)
- Contains D- & L- amino acids
- They both contain an amino acid known as **Ornithine (Orn)**, which is derived from arginine.



Ornithine (Orn)



Gramicidin S



Tyrocidine A

VI. **Aspartame (L-Aspartyl-L-phenylalanine methyl ester)**

- It is a dipeptide (L-aspartic acid and L-phenylalanine) where the C-terminus of phenylalanine is modified by a methyl group.
- They are in the L configuration.
- It is a sweetener and is sweeter than sugar.
- If the L- constituents of aspartame were replaced by their D- counterparts, aspartame would taste bitter instead of sweet.
- Individuals suffering from **phenylketonuria (PKU)** should not digest aspartame.
    - PKU is caused by a defective phenylalanine hydroxylase enzyme.
    - Instead of converting phenylalanine to tyrosine, individuals suffering from PKU convert phenylalanine into phenylpyruvic acid.
    - Phenylpyruvic acid accumulates which causes mental retardation.
    - An alternative of aspartame is known as alitame. (contains alanine instead of phenylalanine)

Now let's talk about protein structure.

So we said that the difference between polypeptides and proteins is that the proteins have defined structures.

Proteins have different structures and some have repeating inner structures, other do not.

The question is: What is the possibilities for polypeptide that's made of 50 amino acids to form a define structure?

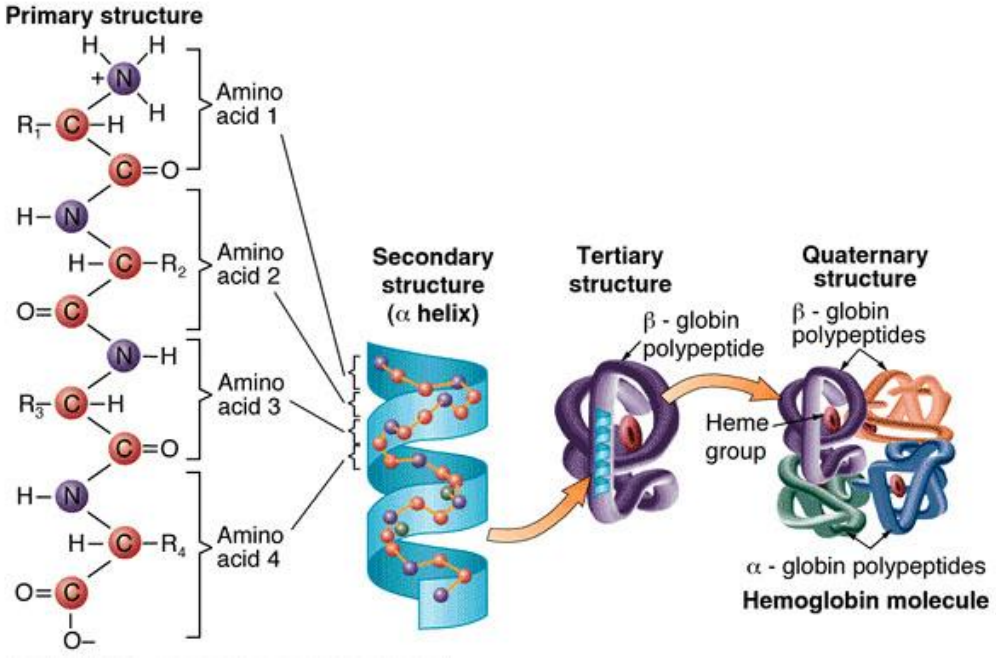
The possibilities are almost infinite. “a gazillions of possibilities”. but in reality is there one structure that can be formed from this polypeptide which is the most stable structure.

- These active structures are known as **native conformations** (the 3 dimensional structure of properly folded and functional protein)

Levels of protein structure:

When we look at protein structures in order to understand them, we have to simplify the structure of row so the scientist divided the complexity of protein structures into 4 levels:

- **Primary structure:** the sequence of amino acid residues.
  so starting from the amino terminus you say this amino acid is number one, amino acid number two, amino acid number three and so on until we reach carboxyl-terminus.
- **Secondary structure:** the localized organization of parts of a polypeptide chain. so primary structure can form organized local structures "certain defined structures depending on sequence of this amino acids “.
- **Tertiary structure:** the 3D structure and/or arrangement of all the amino acids residues of a polypeptide chain.
  and it is show the distribution of amino acids in the space.
- **Quaternary structure:** some proteins are made of multiple polypeptides crosslinked (connected) to each other. These are known as **Multimeric proteins** so quaternary structure describes the number and relative positions of the subunits in a multimeric protein.

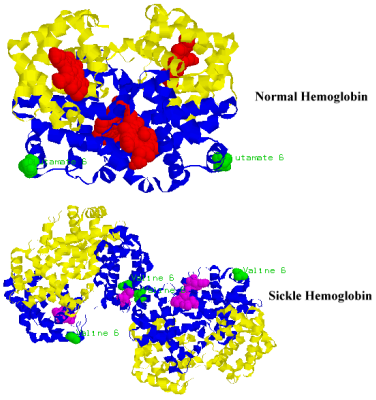


What is the primary structure? Simply, it is the order in which the amino acids are covalently linked together by peptide bond.

Very important information: The primary structure of a protein determines the other levels of structure.

So it determines the secondary structure, tertiary structure and quaternary structure as well.

An excellent example to show you and illustrate the importance of primary structure is sickle cell anemia which basically a change in just one amino acid that exists in the 6th position of the hemoglobin molecule. (Glu becomes Val)

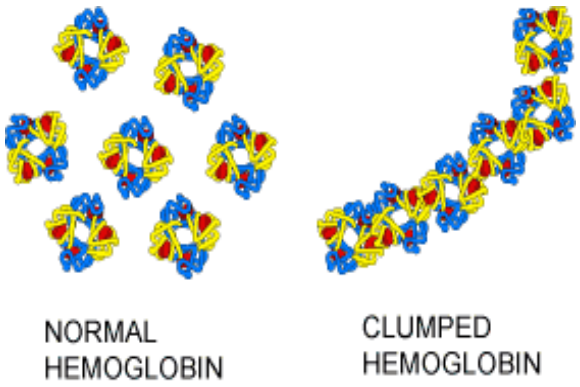


What type of amino acid is Glutamate? Negatively charged.

What type of amino acid is Valine? Non-polar aliphatic.

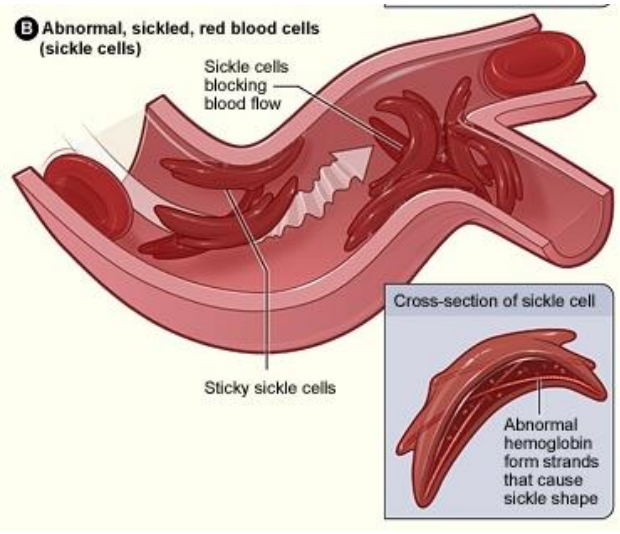
That's change the structure of the whole protein.

When Glutamate changes to Valine the structure of hemoglobin changes totally resulting in connection
or binding or interaction between two hemoglobin
molecules and that results in an array of hemoglobin
molecules linked to each other .



So instead you having individual hemoglobin molecules independent to each other, they cluster, aggregate, form large structure.

Is that important ? definitely yes, because just imagine , you have one RBC having millions of hemoglobin molecules and these hemoglobin molecules cluster together, this change the shape of whole cell, so instead you have RBC that is rounded, you have one that's look sickle (منجل) , like crescent and that's result in accumulation and aggregation of these RBCs

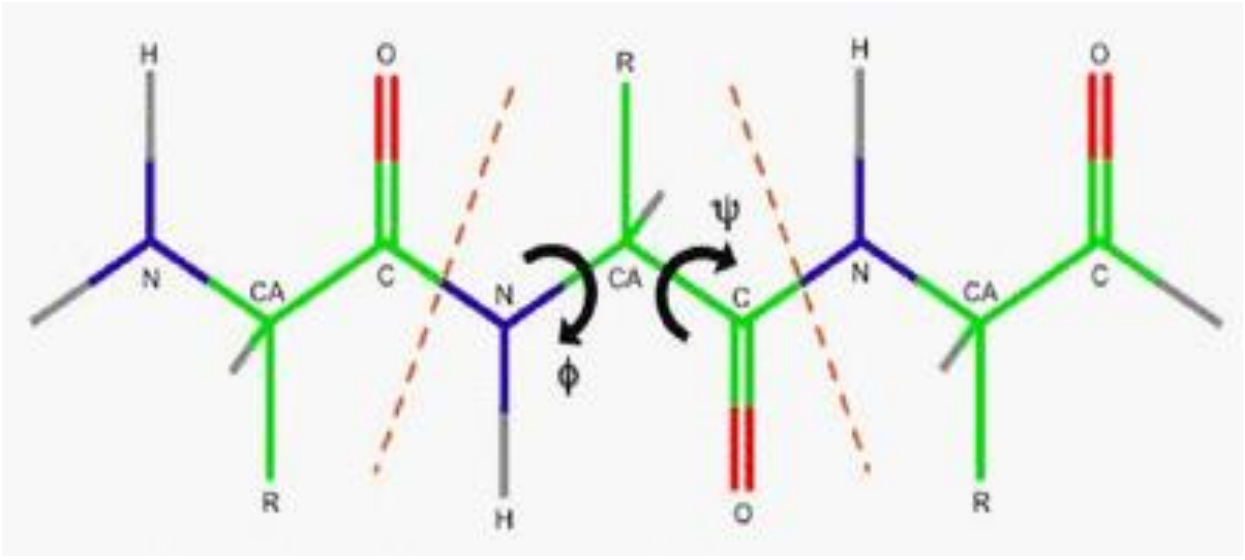


resulting in blocking blood vessels, so there is no O_2 deliver .

Now let's talk about secondary structure.

The two bonds within each amino acid residue freely rotate.

- The bond between α – carbon and the amino nitrogen.
- The bond between α – carbon and carboxyl carbon.



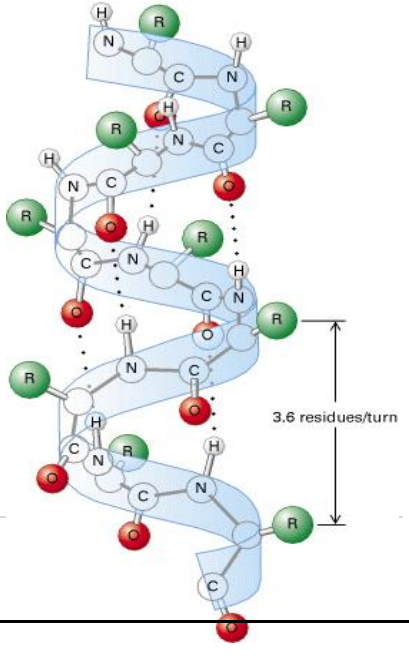
There are 4 types of secondary structures:

- Alpha helix
- Beta-pleated sheet
- Turns
- Loops

We will start with alpha helix.

A helix just like in DNA looks as spring, the alpha helix is define type of helix and that's why we call them (α – helix) to distinguish them from other helixes .

- Looks like a helical rod.
- The helix has an average of 3.6 amino acids per turn.
- The pitch of the helix (the linear distance between corresponding points on successive turns) is 5.4 A° (1 A° = 10^{-10} m)
- It is very stable because of the linear hydrogen bonding within these amino acids so all structure is stable.



There are some amino acids <u>not</u> found in α helix:

1) Glycine: because it's too small.

2) Proline: It is breaks alpha helixes and usually exist in the end of alpha helices, why?
- No rotation around N – Cα bond, his nitrogen is tertiary nitrogen it is link to 3 carbons which forms a peptide bond.

- No hydrogen bonding of α – amino group so it is rigid amino acid.

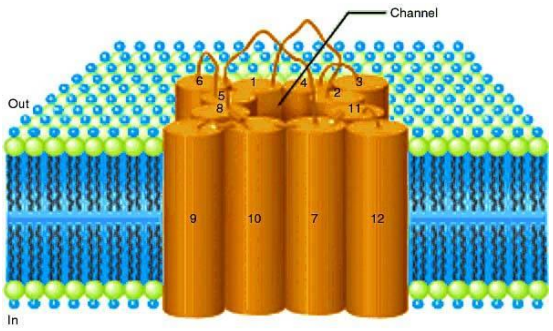
3) Close proximity of a pair of charged amino acids with similar charges, this is cause repulsion between different R groups.

4) Amino acids with branches at the β – carbon atom (Valine, threonine, isoleucine).

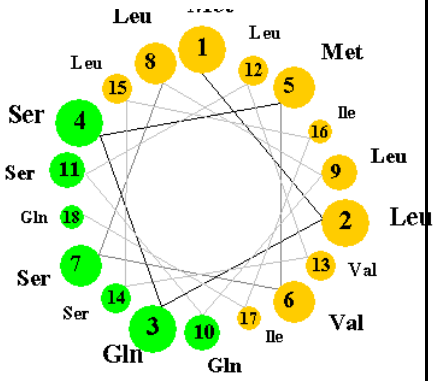
So the question is why when we have branches at β – carbon atom, alpha helixes not favorable ?? because there is repulsion between R groups.

There is special form of alpha helixes known as **amphipathic α helices**.

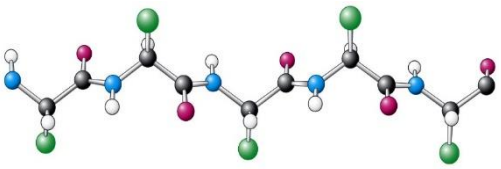
These exist in channel proteins, they form an opening within the cell, this opening allows for entry molecules like ions for example.



So what do we mean by amphipathic α helices?
It is alpha helix whereby if you look at R groups from the top , on one side you have hydrophobic R groups , on the other side you have hydrophilic R groups , so they organized in a certain way whereby you have hydrophobic (non-polar) R groups exposed to the fatty acids of membrane and hydrophilic (polar) R groups exposed to inside of the channel because these amino acids attract ions by having R groups that's charged or polar . if you have hydrophobic R groups, you will have repulsion of these ions.



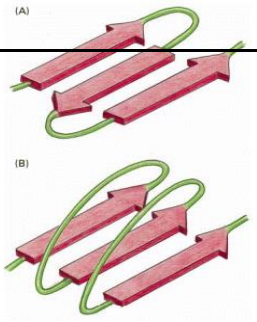
Another secondary structure known as β – sheet and its formed from β – strands. It is look like Zig-zag structure.



Notice that R groups in green are in trans-orientation.

β – sheet: Multiple β – strands on top of each other (side by side) that's are hydrogen bonded .

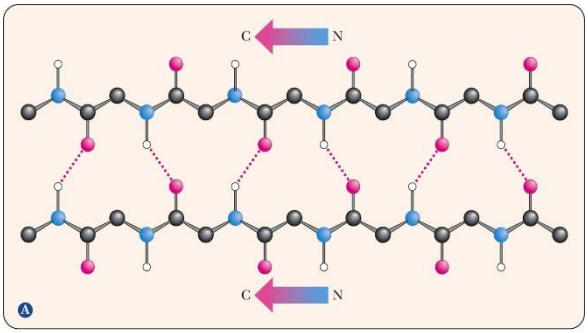
Now these β – sheets can be in two forms and these are:



A) Anti – parallel sheet: the β – strands are in opposite direction.

B) Parallel sheet: the β – strands are in same direction.

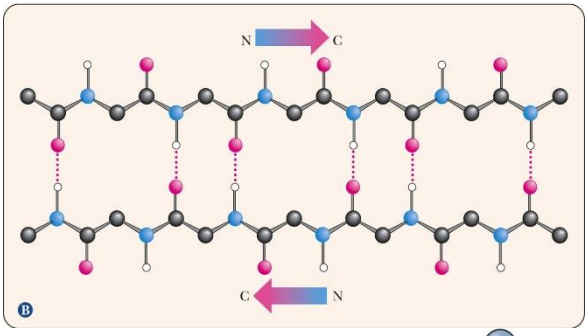
Both make hydrogen bonds but anti parallel is more stable than parallel one because the hydrogen bonds are perpendicular and linear.



So a protein can have combination of β – strands (parallel and anti-parallel) .

Effect of amino acids:

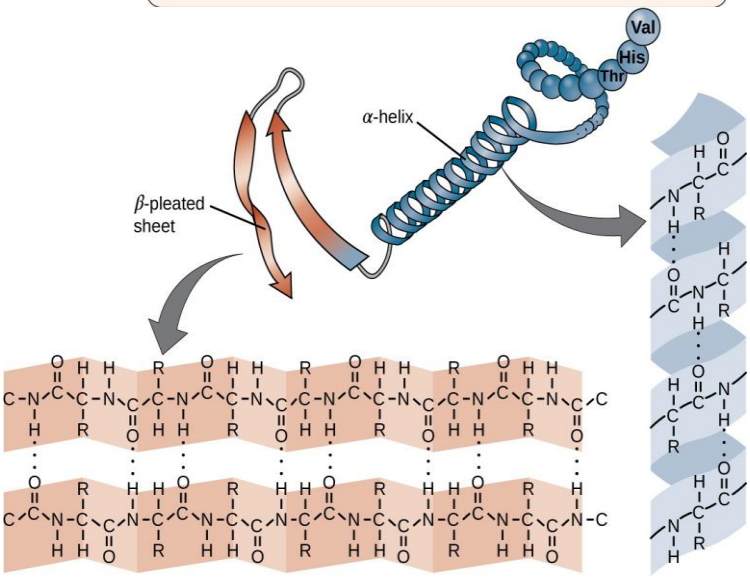
- Valine, threonine and isoleucine with branched R groups at β – carbon and the large aromatic amino acids (phenylalanine tryptophan and tyrosine) tend to be present in β – sheets.
- Proline tends to disrupt β – strands.



Now, how they are illustrated?

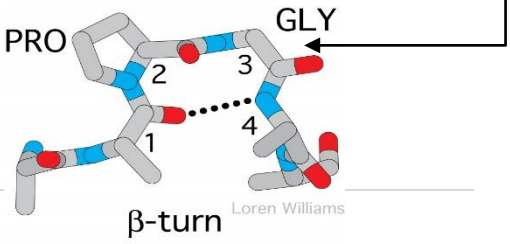
Simply, β – sheets like arrows.

α – helices like springs.



β – turns (hairpin bend): U-shaped secondary structures and they are compact.

It is made from 4 amino acids usually proline exist in number 2 and glycine in number 3 why? Because proline is rigid amino acid so it is breaks the smooth structure of this polypeptide and glycine is small amino acid that's fits on this corner allowing for polypeptide to turn fully, also it is stabilized by hydrogen bonding between amino acid number 1 and 4.



That's all Folks!