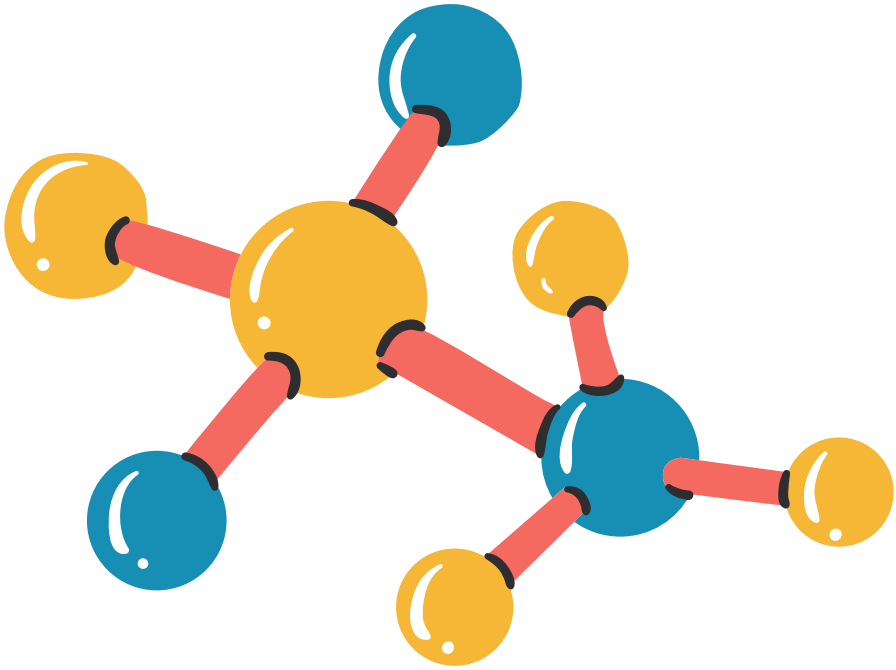
Sheet no. 17

Biochemistry



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In the last lectures we took the common 20 amino acids and their structures , which are used to build up proteins in our bodies .

↳ So, amino acids are the building blocks { monomers } used to build a polypeptide that eventually become proteins .

* Remember that the general structure of amino acids is : a Carbon atom that is connected to 4 different groups

1) Hydrogen 2) Carboxylic group (COOH) 3) Amine group (NH2) 4) R group

the reaction between amino acids to make a polypeptide happens between these 2 groups

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* in this lecture there are 2 major concepts :
① Formation of a polypeptide ② Examples of functional and exceptional peptides

Formation of a polypeptide

Definitions and concepts

* A residue: each amino acid in a (poly)peptide

↳ When we say amino acid residue , then we are talking about an amino acid that is contained as a unit in a polypeptide or protein

* Dipeptide, tripeptide, tetrapeptide, etc.

↳ Dipeptide : contains 2 amino acids
Tripeptide : contains 3 amino acids
Tetrapeptide : contains 4 amino acids

* Oligopeptide (peptide): a short chain of 20-30 amino acids

* Polypeptide: a longer peptide with no particular structure

* Protein: polypeptide chain/or chains with an organized 3D structures

- if the protein contains 1 polypeptide , that means it has only 1 free amine group and 1 free carboxylic group.

- if the protein contains more than 1 polypeptide , that means it has more than 1 free amine group and more than 1 free carboxylic group. However , the number of free amino groups should match with the number of free carboxylic groups.

* The average molecular weight of an amino acid residue is about 110

* The molecular weights of most proteins are between 5500 and 220,000

↳ no. of amino acids per one protein almost between (5500/110 = 50 and 220,000/110 = 2000)

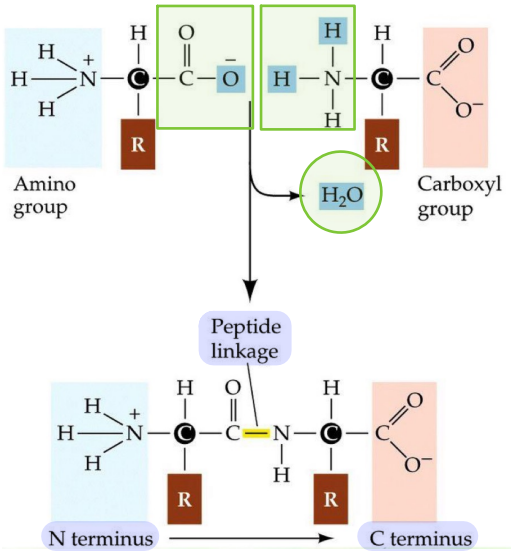
* We refer to the mass of a polypeptide in units of Daltons (Da) or (kDa = 1000 Da)
- A 10,000-MW protein has a mass of 10,000 Daltons (Da) or 10 kilodaltons (kDa)

Peptide bond

* Amino acids are joined together by a chemical reactions (condensation ; dehydration reactions) that eliminate water and create joins between them called **peptide bonds**.

** the reaction occurs between the amine group of one amino acid and the carboxylic group of the second amino acid.

↳ when the reaction happen the nitrogen atom of the amine group is covalently linked directly to the carbonyl carbon



* Chemically, peptide bond is an amide bond , but when it is inside proteins it is called peptide bond.

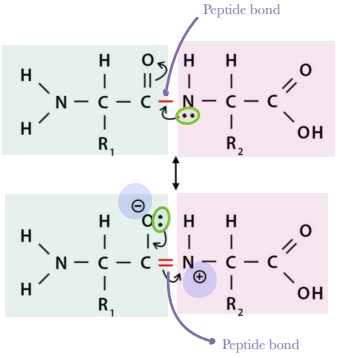
* notice that amine group loses 2 hydrogen atoms , and the carboxyl group loses an oxygen atom.

* Features of the peptide bond :

- the peptide bond has a resonance structure

Because ↳ the nitrogen is able to donate its lone pair of electrons to the carbonyl carbon and push electrons from the carbonyl double bond towards the oxygen, forming the oxygen anion.

↳ This makes the peptide bond to alternate between the single and double forms.

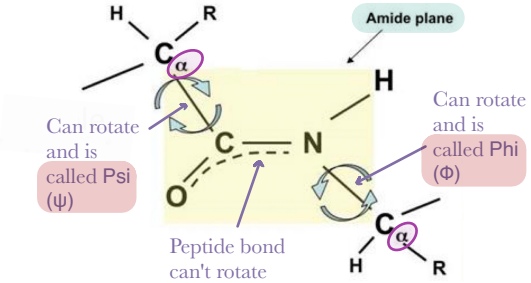


* So, Resonance structure makes peptide bond :

1) Zigzag structure
2) Double bond { Planar, Charged, Rigid, Un-rotatable }

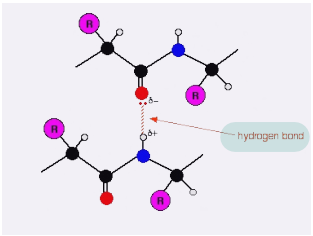
NOTE :

the peptide bond itself is un-rotatable ,but the rotation could be happened within the amino acids because the alpha carbons in the peptide backbone have the ability to rotate freely around their bond axes.



3) it is stronger than an ordinary single bond because of the resonance stabilization.

4) Hydrogen bonding (Except proline).



↳ between the hydrogen of amine group and oxygen of carbonyl group.

↳ Proline can't form hydrogen bonding because the nitrogen of Proline is occupied by three covalent bond so it doesn't have hydrogen that can be donated into hydrogen bonding { it is the only amino acid that doesn't have H-bond donor is Proline }.

* NOTE:

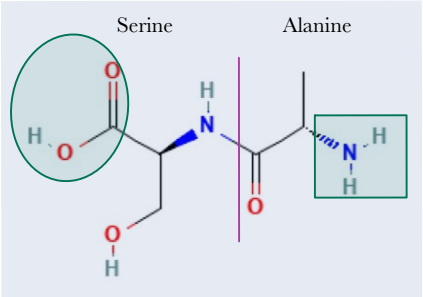
to synthesize a polypeptide in a chemical solution , it doesn't matter if the second amino acid is added to the free amine group or to the free carboxylic group . But! for the polypeptide that is being translated in the ribosomes , the new amino acids are added , specifically , to the carboxylic group.

* Doctor asked , if we have 2 amino acids and we want to make a dipeptide , how many possibilities to combine the 2 amino aids with ?

the answer is two possibilities

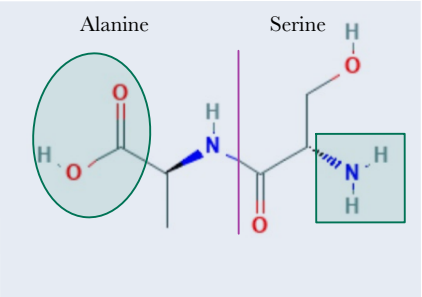
Explanation ↳ for example ; if I want to join Alanine with Serine

First sequence Ser - Ala



here the free group in :
serine is COOH → pKa = 2.21
alanine is NH3 → pKa = 9.69

Second sequence Ala - Ser



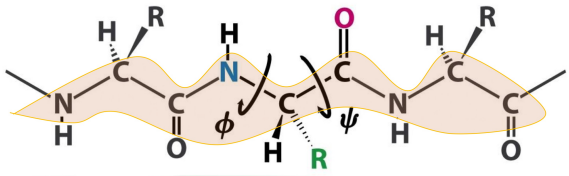
here the free group in :
serine is NH3 → pKa = 9.15
alanine is COOH → pKa = 2.34

- SO , the sequence matters → because different sequences will produce different free groups , and this will affect the pH value because of the different pKa values for each amino acid. Also this will affect the protein folding .

Backbone, orientation and directionality

* The Backbone :

it is a repetitive sequence of α-amide N, the α-C, and the α carbonyl C atom .

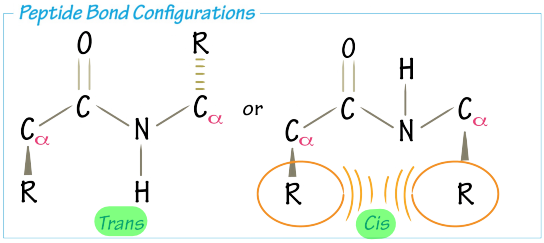


* The Orientation of side chains (R) :

- there are 2 configurations → trans and cis

① trans configuration ;
the R groups are in different orientation like up , down , up , down , etc.

② cis configuration ;
the R groups are in same orientation like up , up , up , up , etc.



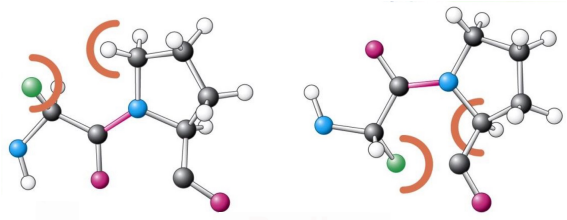
- most peptides exist in the trans configuration to reduce steric repulsion , which increases the stability and reduces the energy for molecules.

- Steric hindrance between the functional groups attached to the alpha C atoms will be greater in the cis configuration.

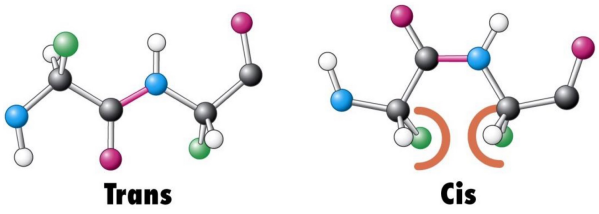
- In proline, both cis and trans conformations have about equivalent energies.

↳ So proline doesn't have any preference for cis or trans orientation because in both ways there is repulsion.

-Proline is thus found in the cis configuration more frequently than other amino acid residues.



Proline

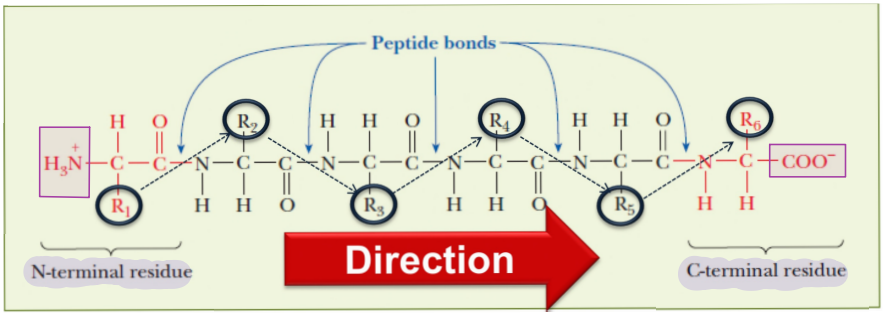


All other amino acids

* The direction :

- The peptide has a polarity (two different ends) the first end is known as a N terminus ,and the last end is known as C terminus ,so we have two opposite ends because the N end is positively charged and the C end is negatively charged (in neutral pH).

↪ always when you are looking at a sequence of amino acids , you should read it from the N-terminus to the C-terminus { from the most left to the most right , if the sequence is represented in the letters code }.



Examples of Functional and Exceptional peptides

* They are physiological peptides that have effects within our bodies , and consist of few amino acids :

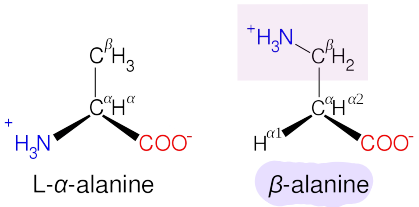
1- Carnosine 2- Glutathione 3- Enkephalins 4- Oxytocin and Vasopressin
5- Gramicidins S and Tyrocidine A 6- Aspartame

Carnosine (β-alanyl-L-histedine)

* It is a naturally occuring dipeptide (alanine , histidine)

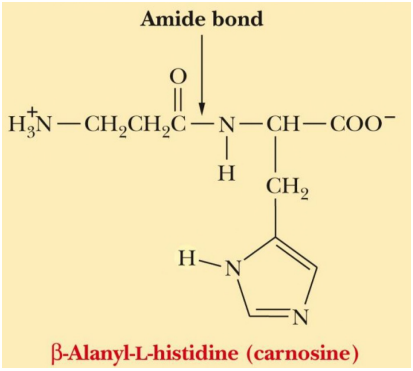
↪ β-alanine

- The amine group is bonded to the β-carbon (notice that the alpha carbon lost its chirality)
- note : it is unusual amino acid



↪ L-histidine

so, Carnosine is called β-alanyl-L-histedine



* It is highly concentrated in muscle and brain tissues.

* Functions :

① Contraction of muscle

② Protection of cells from ROS (radical oxygen species) and peroxides. { anti-oxidants)

Remember : molecules that contain rings in their structure acts better as anti-oxidant than open chain structure .

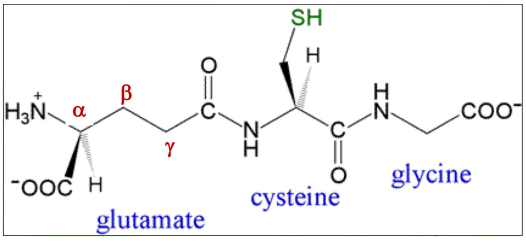
↪ that is why carnosine is an excellent anti-oxidant , because of the imidazole ring in the histidine amino acid.

Glutathione: γ-glutamyl-L-cysteinylglycine

* it is a tripeptide

↳ L - γ - glutamic

it is called gamma because the gamma carboxylic group doing the peptide bond.



↪ L - cystiene

↪ L - glycine

* Function :

Acts as a scavenger for oxidizing agents (Some oxidizing agents are harmful and play a role in the development of cancer) by reacting with them.

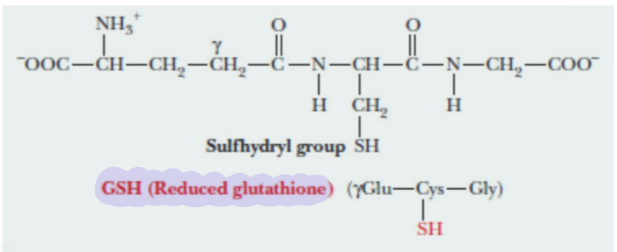
- it is the most common and prevalent anti-oxidant in the body.

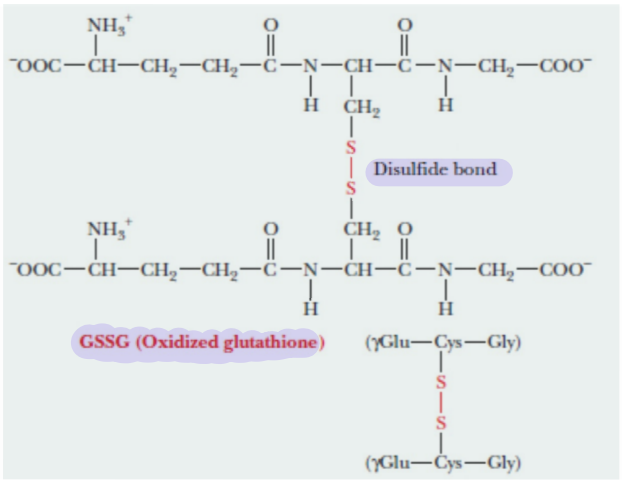
↪ that does not make sense, because it doesn't have a ring in its structure

↪ However it has the thiol group (SH) that makes it good anti-oxidant.

↪ the mechanism :
the SH group donate the hydrogen atom with its electron to the free radical (so the SH group is converted from the reduced form to the oxidized form)

↪ 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.



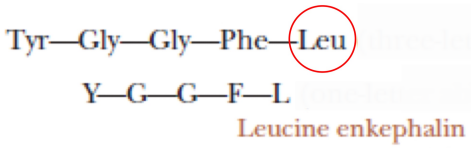


* The oxidized form of the glutathione can revert to the reduced form enzymatically.

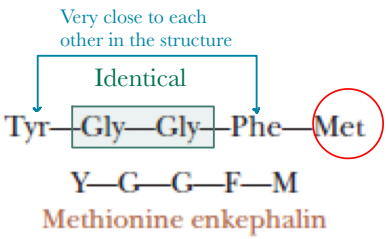
Enkephalins

* they are 2 classes of naturally occurring pentapeptides [They differ only in their C-terminal amino acids] :

1) Leucine enkephalin



2) Methionine enkephalin



* they are found in the brain.

* they function as analgesics (pain relievers).

- in our body there is a threshold for the pain

↳ if you cross this threshold you will feel pain

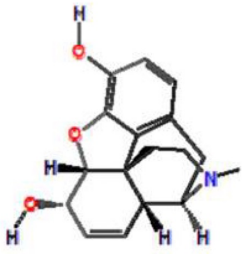
↳ if you below it you won't feel pain , because of enkephalins which are being synthesized in the body ,that work as analgesics (they bind to special receptor)

- The aromatic side chains of Tyr and Phe in these peptides play a role in their activities.

* There are similarities between the three-dimensional structures of opiates, such as morphine, and enkephalins.

So, ↳ opiates bind to encephalin receptors in the brain to produce their physiological activities.

- Morphine is a drug that is given after surgeries to block the huge pain.



Morphine

Enkephalins

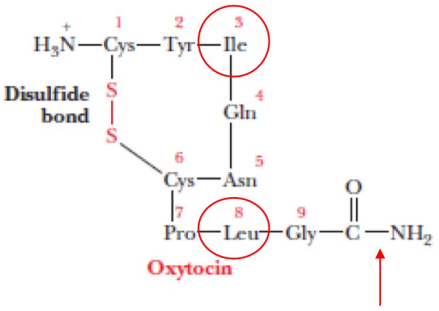
Oxytocin and Vasopressin

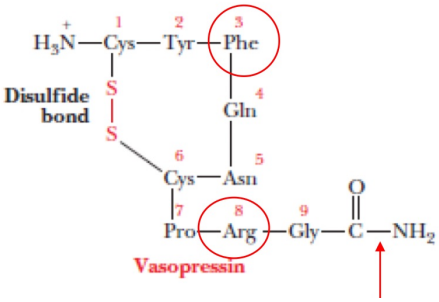
* they are nanopeptide Hormones with cyclic structures due to S-S link between Cys residues at positions 1 and 6.

* they have 7 identical amino acids in the type and sequence ,but they differ in 2 amino acids at position 3,8 .

  ↪ Oxytocin has isoleucine (3) and leucine (8)

  ↪ Vasopressin has phenylalanine (3) and arginine (8) .





* Both have an amide group (rather than a free carboxyl group) at the C-terminal end.

* both are secreted from the hypothalumus and stored in the posterior pitutary gland.

Oxytocin induces labor in pregnant women by controlling contraction of uterine muscle and stimulates the flow of milk in a nursing mother

During pregnancy, the number of receptors for oxytocin in the uterine wall increases.

As the cervix stretches, sending nerve impulses to the hypothalamus as a positive feedback to release more oxytocin by the posterior pituitary gland.

Vasopressin controls of blood pressure by regulating smooth muscle contraction.

Vasopressin is released by the action of the hypothalamus on the posterior pituitary.

Vasopressin stimulates water reabsorption by the kidney (an antidiuretic effect) resulting in water retention and blood pressure increase.

* Note about Vasopressin: its concentration increases at night

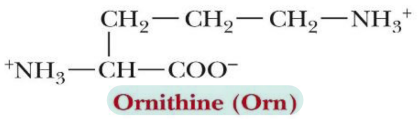
Gramicidins S and Tyrocidine A

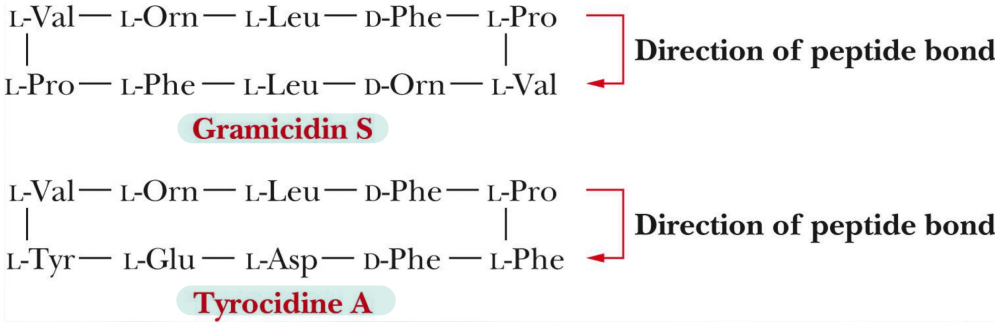
* They are cyclic decapeptides formed by the peptide bonds

* Two cyclic decapeptides produced by the bacterium Bacillus brevis.

* Both contain D-amino acids and L-amino acids.

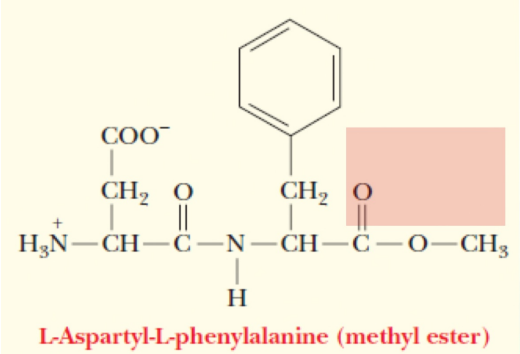
* Both contain the amino acid ornithine (Orn), which does not occur in proteins (it is important in urea cycle).





Aspartame : L-Aspartyl-L-phenylalanine (methyl ester)

* it is a dipeptide :
  - ↪ L-aspartic acid
  - ↪ L-phenylalanine
  - ↪ It has a methyl group on the C terminus of the dipeptide.



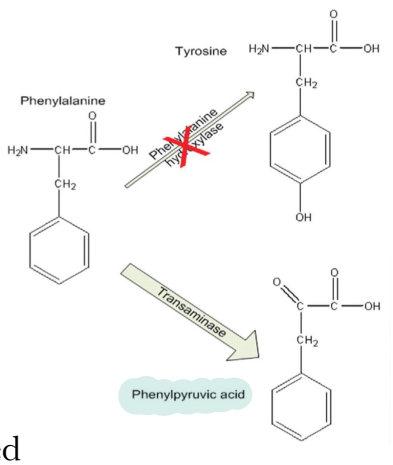
* It's an artificial sweetener and its used as a substitute for sugar.
  - it is 200 times sweeter than sugar.

* 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 should not be given to individuals with a condition known as Phenylketonuria (PKU)

Phenylketonuria (PKU)

* PKU is a hereditary "inborn error of metabolism" caused by defective enzyme, phenylalanine hydroxylase.
  - phenyalanine hydroxylase converts the phenylalanine into tyrosine.



* It causes accumulation of **phenylpruvate**, which causes mental retardation.

* Sources of phenylalanine such as aspartame must be limited

* A substitute for aspartame, known as alatame, contains alanine rather than phenylalanine.