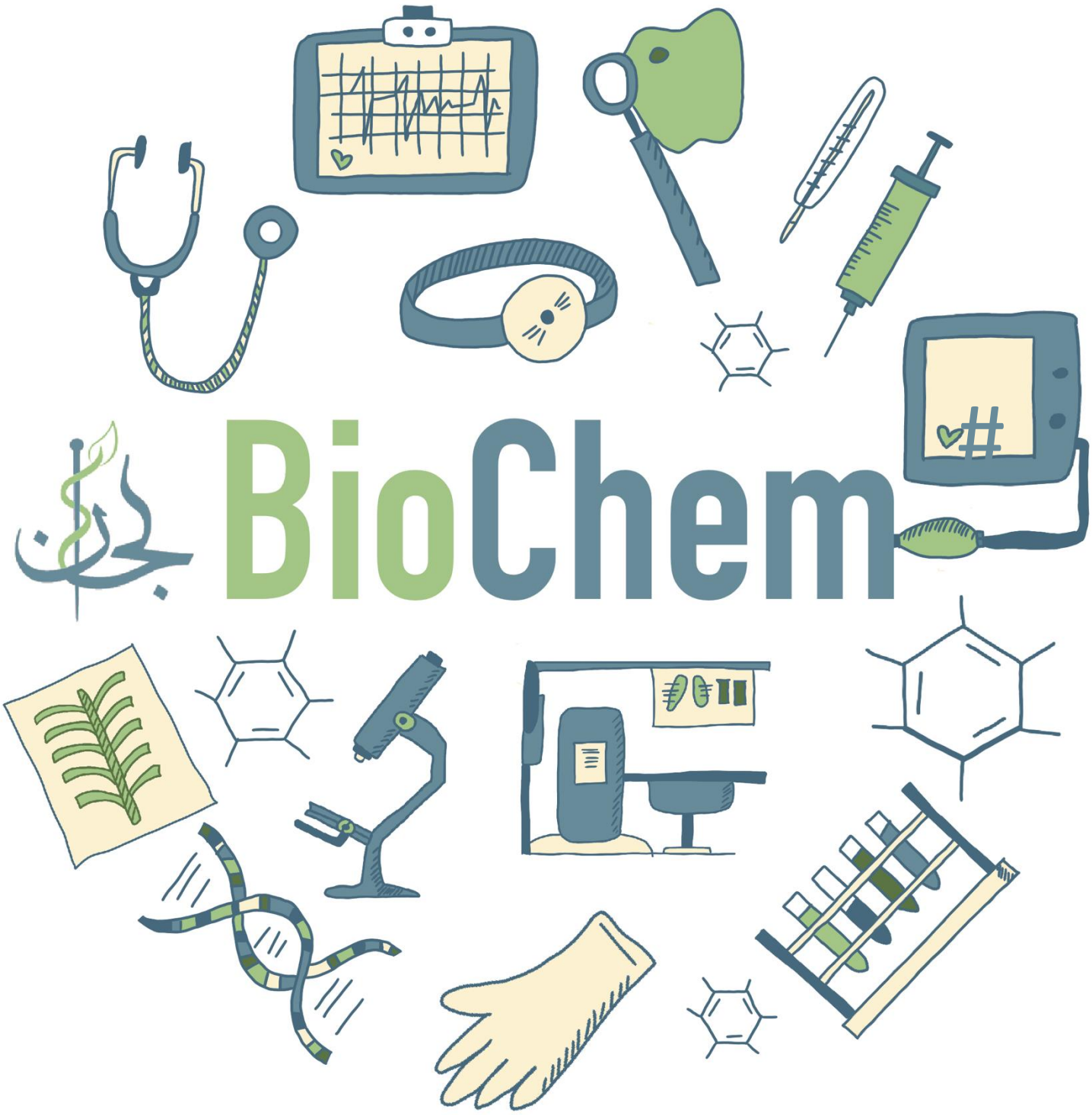

BioChem

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Amino acids

-Protein structure and function.

1- Proteins come from the Greek word: proteios, which means primary (important).

2- 50% of body's dry weight is protein indicating that proteins are very important.

What is the difference that proteins carry, and carbohydrates and lipids don't?
-their ability to change their structure upon binding to other molecule
What happens is the formulation of the protein within a certain structure, and it can change its shape upon binding to other molecules thus having various functions accordingly.

Note: when a molecule binds to a receptor (receptors are proteins) ➡ the receptor changes its shape (its conformation) conferring another change in a molecule inside the cell.
Similarly, enzymes work in the same manner. When an enzyme binds to its reactant, the enzyme will change its own shape (This is how catalysis occurs).
This also explains why we have more proteins compared to carbohydrates and lipids.

3- proteins deliver wide range of function:

They can work like:

- Enzymes
- Hormones
- storage
- transport
- giving the structure of the body (Like collagen)
- protective role (Like immunoglobulin that works in the defense mechanism of the body)
- contraction (movement of muscles)

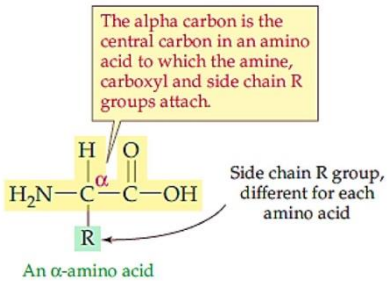
Protein structure and function

TYPE	FUNCTION	EXAMPLE
Enzymes	Catalysts	*Amylase*—begins digestion of carbohydrates by hydrolysis
Hormones	Regulate body functions by carrying messages to receptors	*Insulin*—facilitates use of glucose for energy generation
Storage proteins	Make essential substances available when needed	*Myoglobin*—stores oxygen in muscles
Transport proteins	Carry substances through body fluids	*Serum albumin*—carries fatty acids in blood
Structural proteins	Provide mechanical shape and support	*Collagen*—provides structure to tendons and cartilage
Protective proteins	Defend the body against foreign matter	*Immunoglobulin*—aids in destruction of invading bacteria
Contractile proteins	Do mechanical work	*Myosin and actin*—govern muscle movement

4-polymers of amino acids.

5-structure of the amino acid (backbone vs. sidechains)

Monomers that constitute the protein are called **amino acids**.



- what do we mean by an amino acid?

the name implies the structure (amino: amine group)
(acid: carboxylic group)

-the general structure of each amino acid:

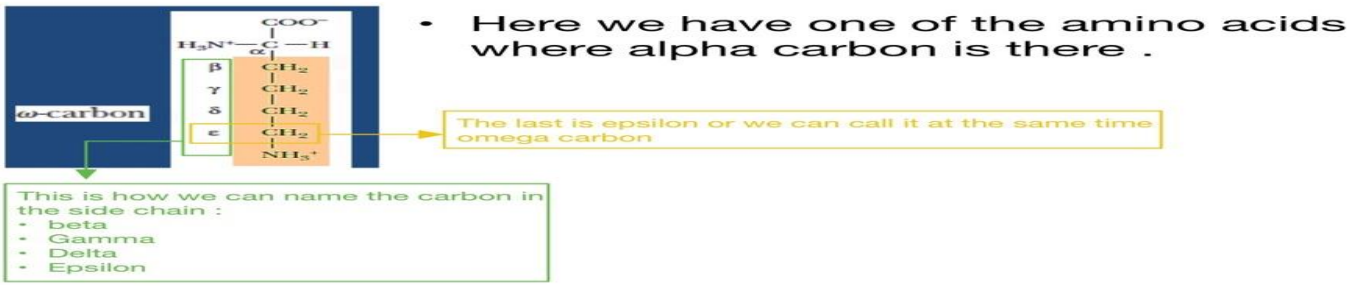
- Carboxyl group
- Alpha carbon
- Hydrogen atom
- Amine group

→ **the backbone** because it is repetitive in each amino acid

- Side chain (R group): a constituent within the structure of the amino acid which differ each amino acid from another.

*Alpha carbon is called alpha because it is the first carbon after the carboxylic group.

when having more carbons in the side chain ➟ You name them accordingly (beta / gamma / delta / epsilon) with the last carbon in the side chain called an **Omega carbon**



what should not be forgotten for good

-there are a lot of amino acids in life: more than 300 amino acids (not all of them within our bodies)

**more than 20 amino acids can be synthesized in our bodies.

-there are 20 encoded by the genetic code (to be more accurate,21 amino acids are incorporated in protein structure even though one of them Selenocysteine is not encoded by the genetic code in the ordinary manner)

-what are these 20 amino acids?

these are encoded by the genetic code which means that those amino acids will be incorporated inside proteins.

mRNA ⟶ encodes proteins; accordingly, the codons represent 20 amino acids. So, we won't find in any protein within our bodies other than those 20 or 21 amino acids

Can we find more amino acids inside our bodies? Yes, but **not in the structure of proteins**.

*An example of non-coding amino acid in our bodies: **citrulline and ornithine** (basic amino acids) are the main constituents of the urea cycle, even if those amino acids aren't in the structure of proteins, without them there isn't a urea cycle (no urine).

*Side note: not all amino acids can be synthesized in our bodies that's why we separate them into essential and not essential amino acids.

-the basis of their classification:

amino acids have a general structure which is
present in each one of them (**the backbone**) and what makes them different from one another is a constituent within their structure called the **side chain (R group)**

Therefore, amino acids are classified according to the R group.

Note:-when looking at the R group, many classifications can be made.one of them is according to the **polarity**

-handedness and chirality (L vs. D)

Are amino acids chiral or achiral?

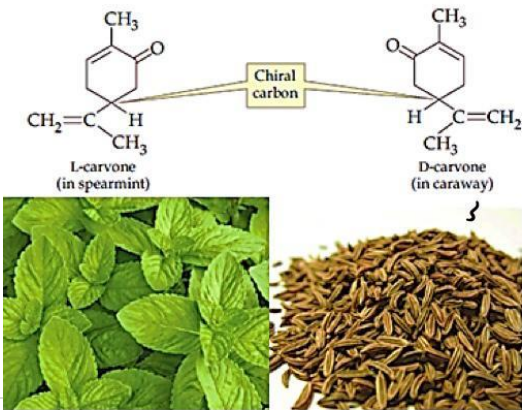
- The carboxyl group carbon ⟶ Achiral (we have a double bond connecting the carbon with the oxygen)
- Amine group ⟶ (no carbon)
- Alpha carbon has:
  - Hydrogen
  - Carboxyl group
  - Amine group

  Three different connections
  - The 4th connection is the one which determines if this alpha carbon is chiral or achiral. So, if it has hydrogen, its achiral. (This is present in only in one amino acid called **glycine** "the smallest amino acid"). But if this hydrogen was replaced by any other group, then we will have a chiral carbon

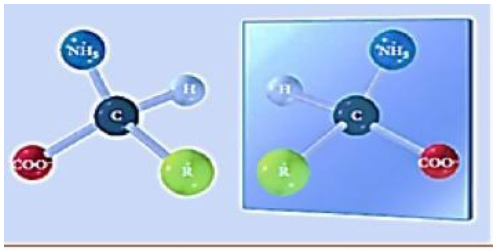
Therefore, we have 19 chiral amino acid out of 20.

chirality endorses function and different properties (physical and chemical).

For example: L and D configurations have different properties
A molecule called carvone has two configurations,
(L-carvone and D-carvone)



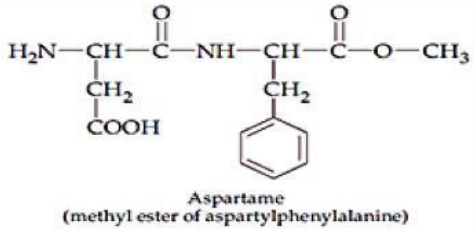
Each of them gives different physical and chemical properties:



L gives spearmint.

D gives caraway.

another example is Aspartame which is the sweetener that is present in a lot of things such as diet coke, diet Pepsi, sugarless gum and diet juice.



Aspartame
(methyl ester of aspartylphenylalanine)

Artificial sweeteners are constituted of two amino acids (**aspartic acid and phenylalanine**) connected to each other.

Both amino acids must be in the L- configuration,
If one of them has a D- configuration, it will give a bitter taste.

(Will be explained later)

Names and codes.

Until now, we have 20 amino acids in addition to an extra amino acid discussed later.

- ✓ you have to memories all the amino acids (presented in the alphabetical sequence). In addition to their three-letter code preferably know the 1-letter code (not required in our exam).

Names and codes

Amino Acid	3-letter code	1-letter code	Amino Acid	3-letter code	1-letter code
Alanine	Ala	A	Leucine	Leu	L
Arginine	Arg	R	Lysine	Lys	K
Asparagine	Asn	N	Methionine	Met	M
Aspartic acid	Asp	D	Phenylalanine	Phe	F
Cysteine	Cys	C	Proline	Pro	P
Glutamic acid	Glu	E	Serine	Ser	S
Glutamine	Gln	Q	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Histidine	His	H	Tyrosine	Tyr	Y
Isoleucine	Ile	I	Valine	Val	V

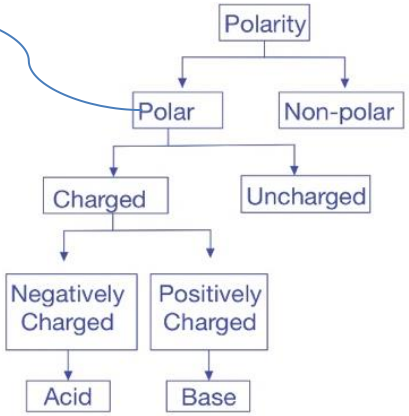
- **The three-letter code**: is the 1st three letters of each amino acid except when 2 amino acids share the same first 3 letters, the code will be different. How?
  Then pronunciation (sound) will play a role.
  For example:
  1-**Asparagine and aspartic acid**: share the first 3 letters, so we coded aspartic acid with ASP and asparagine with ASN
  2-**glutamic acid and glutamine**: glutamic acid with GLU and glutamine as GLN.

** The 1-letter code is not a universal code: the amino acid is coded by its first letter, when it's mutual, we use pronunciation.

- ✓ we are required to know the structure of the 20 amino acids that will be explained in a minute.

Structure of amino acids:

- How do we know the polarity?
If it has oxygen, nitrogen, or sulfur.



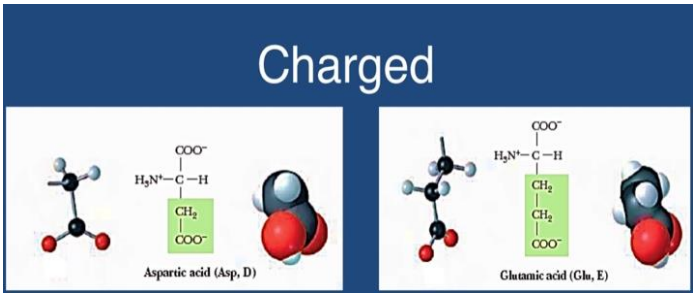
First, the **charged amino acids**.
There are **5** charged amino acids.

- **negatively charged amino acids (acidic amino acids)** :
  Aspartic acid and Glutamic acid.

Regardless of the backbone which is shared in between all the amino acids, we are concerned with the R groups in their structure.

Their name implies their structure "Acid". So, it must have a carboxylic group in its R group.

the only difference between them is that ASP has one carbon connected to its carboxylic group within the R group while GLU has two Carbons connected to it .



-What happens if we remove the O- from the aspartic acid replacing it with an amino group(uncharged)?

:this will lead to the formation of an amide bond and that's how we synthesize the amino acid Asparagine.

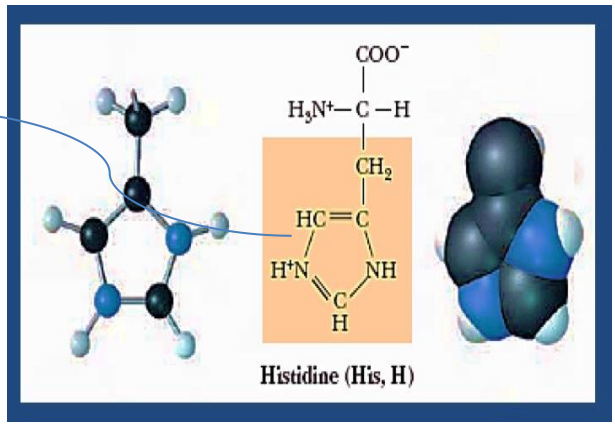
this process is called **amidation** and the product molecule is described as polar, uncharged called asparagine (which is different by having an **amino group connected to its carbonyl group** where the o- is not there anymore)

aspartic acid → (**amidation**) → **asparagine**
glutamic acid → (**amidation**) → **glutamine**

Asparagine and glutamine are the first 2 polar uncharged amino acids

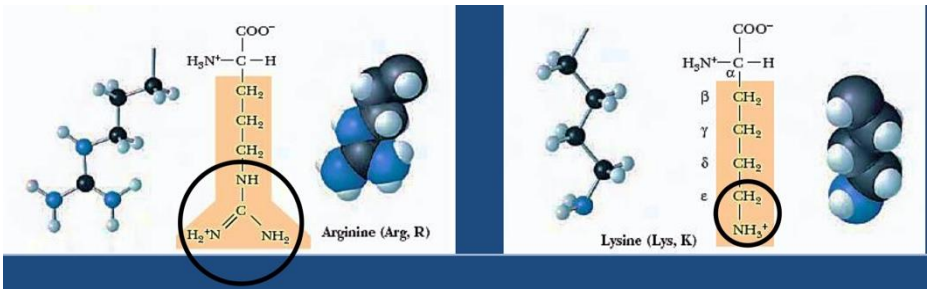
- **positively charged amino acids (basic amino acids).**
  (it must have an amine group within their side chain)
  *The easiest one to know is histidine -His- because it has a cyclic structure (5 membered ring -called imidazole- in its R group which contains two nitrogen atoms, one of which is positively charged)

Here we have a resonance structure; the double bond will keep alternating between the two nitrogens so the positive charge will be present in one of them



the remaining 2 basic amino acids are Arginine and Lysine

*it's very easy to differentiate in between these two amino acids:



-Arginine has what we call a **guanidino group**:

carbon is connected to 3 amino groups one of them at a certain time has a double bond structure which implies the positivity of the amino group (**resonance formation will keep rotating**).

-Lysine is an aliphatic structure in an open chain form

(4 carbons connected at the end with one positively charged amino group)

Now, the polar uncharged amino acids:

Till now, we know 5 polar charged amino acids Asp, Glu, His, Arg, Lys.

And the first two uncharged amino acid (but polar) are Asn, Gln which we talked about previously.

So, we now know 7 amino acids out of 20.

We said before that **polarity is due to oxygen, nitrogen, and sulfur.**

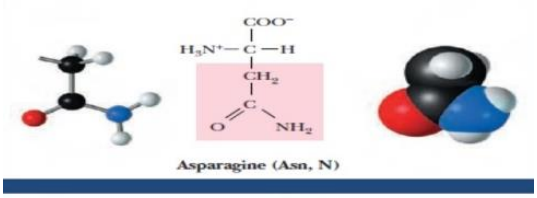
we know by now that nitrogen induces polarity to 2 amino acids which are Asn and Gln.

What about other atoms?

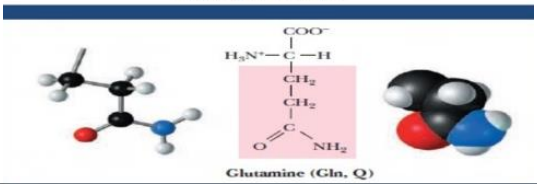
Oxygen induces polarity to **3** amino acids and sulfur induces polarity to **1** amino acid.

So, **we will have 6 amino acids in the polar uncharged group** (2 because on nitrogen, 3 because of oxygen and 1 because of sulfur).

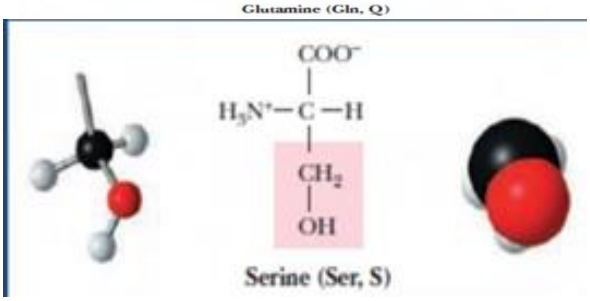
- **Asp and Glu** have the same process when **amidated,** we remove O^- and replace it with an amine group resulting the production of **Asn , Gln** respectively. The source of polarity is **nitrogen**.

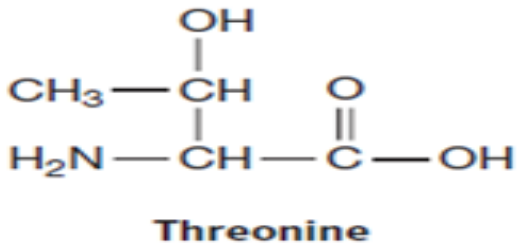


- **Serine** has one carbon atom connected to a hydroxyl group in its side chain. What induces polarity is **oxygen**.

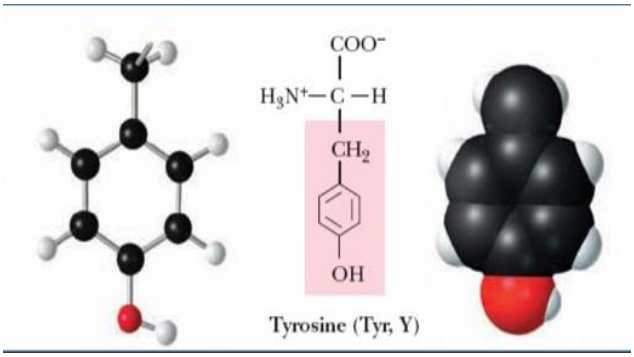


- **Threonine** has on carbon atom connected to one hydroxyl group and one methyl group within its R group . The source of polarity is again **Oxygen**.

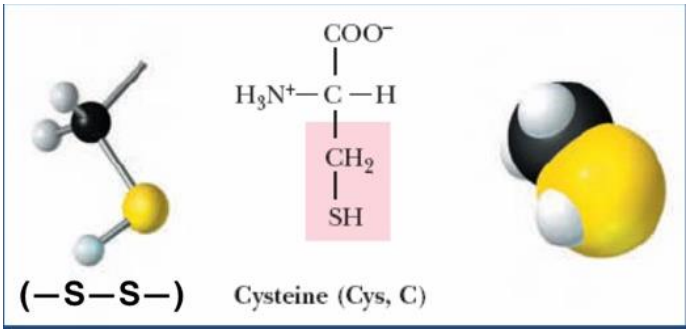




- **Tyrosine** has one carbon atom attached to a benzene ring that is attached to a terminal hydroxyl group. However, **its polarity it due to Oxygen** (Without the hydroxyl group, it's not a polar molecule because neither CH_2 nor Benzene are polar).



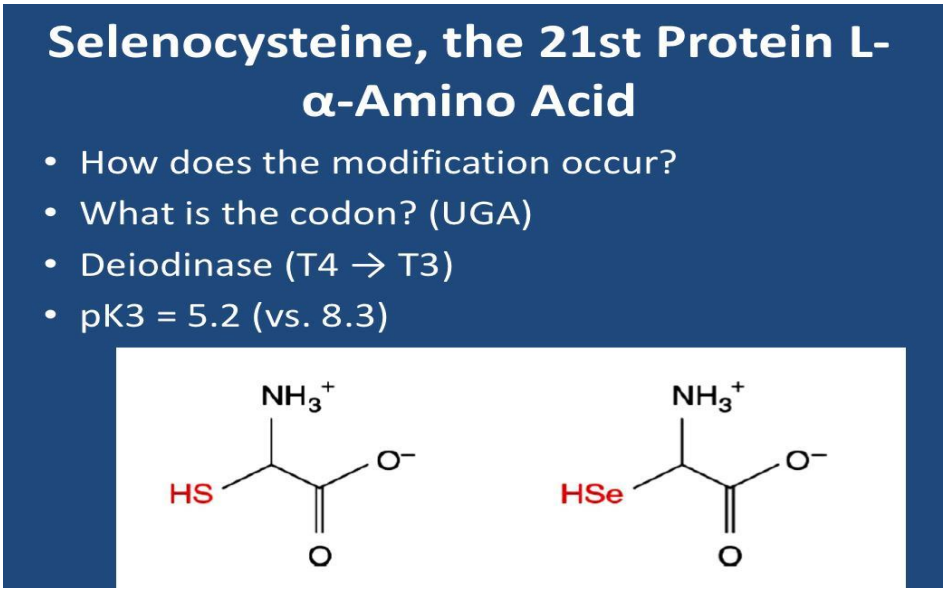
- **Cysteine** has 1 carbon connected to a thiol group in its side chain
  (Thiol group is sulfhydryl group, terminal in the molecule)



The 21st amino acid called is selenocysteine

How is Selenocysteine different from cysteine?

It's not connected to a sulfur; it's connected to a **selenium atom.**



NOTES ABOUT SELENOCYSTEINE:

A) Selenocysteine is not encoded by the genetic code. Also, it's not a modification of cysteine as a post translation modification.

selenocysteine is added into the growing polypeptide chain as an **amino acid**.

How is it added while not having a specific codon? **It uses the stop codon which is called UGA**

Recall: when we have a stop codon, it should terminate the process of translation,

however, sometimes **this stop codon (UGA**) is followed by an untranslated region (certain stem loop structure) that a **tRNA** that carries selenocysteine can identify, so accordingly UGA will not be at that time a stop codon, but will be translated into the anticodon of selenocysteine, **As a result selenocysteine will be inserted to the growing polypeptide chain .**

- Deiodinase (T4 → T3)

Selenocysteine is present in many proteins within our bodies, such as: **deiodinase** which converts the **T4 (Tetraiodothyronine)** into the more active form which is the **T3 (Triiodothyronine)**

- pK3 = 5.2 (vs. 8.3)

Compared to the cysteine, the pka of selenocysteine is less by three ph. units.

. Pka in the cysteine is around 8.3

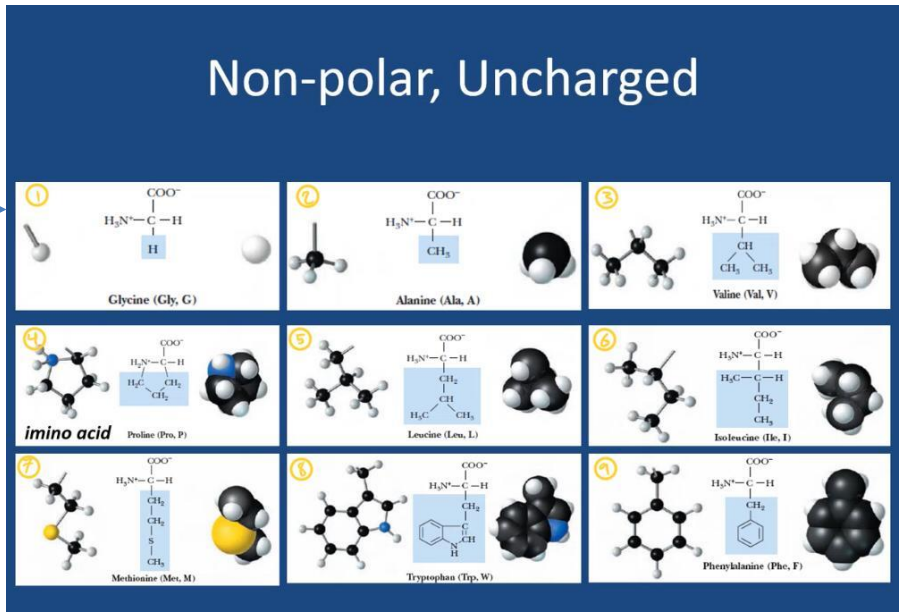
. Pka in the selenocysteine is around 5.2

the non-polar & uncharged ones:

. **We have non-polar amnio acids**:

- The first one is the one which has only hydrogen in its side chain, the achiral amino acid which is **Glycine** (Gly,G)

** some textbooks classify them with polar ones and others classify them as non-polar ones, here we should follow what the doctor gives us "they are non-polar "



What else makes the molecule non-polar? The hydrocarbon chains

- it's either a hydrogen in the side chain as **Glycine**, (Achiral as well and the smallest amino acid because it only has H inside chain) (1)

- it might have one carbon, so the side chain is CH3 only, this is called **Alanine** (2)

- it might have 3 carbon units within its side-chain and in this case it is called **Valine**, it is a **branched** amino acid (3)

- there are also 2 molecules that have four carbons inside the R group, (**branched**):

  - one of them is called **Leucine** (5)
  - the other is **Isoleucine** (6)

** we are not required to differentiate between them, but they are **isomers** to each other

Remember: (tyrosine has one carbon, benzene ring, oh group in its side chain) and what endorses the polarity is the presence of the oh group, - if we don't have this oh group-
we will have another amino acid which is called **phenylalanine** (9)

***Why do we call it phenylalanine?**

because its side chain contains alanine (has one carbon in its side chain) + it has phenyl group (benzene ring).

- the bulkiest amino acid is called **Tryptophan** (8) as it contains one carbon and two rings (a 5 membered ring and a 6 membered ring connected to each other)

***What makes cysteine polar ?**

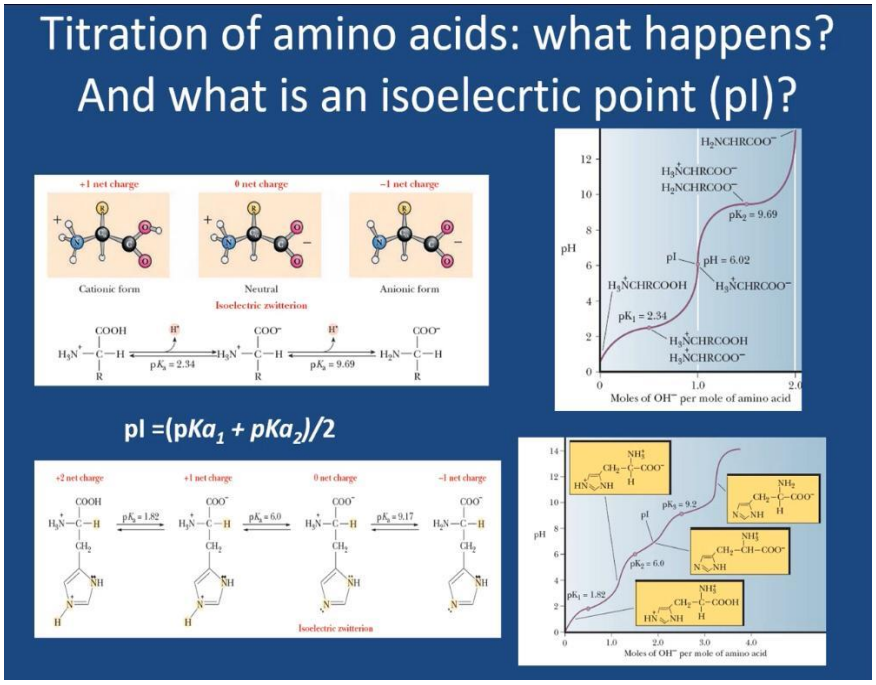
is the presence of a terminal sulfur group (thiol).However, if sulfur is connected from both sides by carbon, (it's not polar anymore) which is the case in **Methionine**

Methionine amino acid, contains within its side chain 2 carbons then a sulfur atom followed by another carbon (7)

Proline, it contains 3 carbons in the side chain and **the last carbon is coming back and making a connection with the nitrogen of the backbone** thus making proline different from the rest of the amino acids, which have their R groups free in space. Therefore, sometimes Proline is called an **imino acid** because it's a **secondary amine (The nitrogen is connected to 2 carbons).** (4)

Recall from previous lectures :-

- that pH is a property of solutions (it can be changed) ,while pKa is a property of a chemical structure (it cannot be changed)
- pKa is defined as the tendency of a given molecule to donate protons to the solution.
- According to the Henderson equation, if pH is higher than the pKa value for the given acid by a one unit different, then the [A-]/[HA] is 10:1 and therefore, we conclude that 91% of the solution contains the conjugate Base, while 9% of the solution contains the acid itself and so on .



- Depending on the number of titratable groups , we obtain the number of titration curves. In each Amino acid , there is at least 2 titratable groups (The carboxyl and amino group). However sometimes the side chain can have a titratable group such as **the 5 charged amino acids as well as Cysteine and tyrosine**

➢ in each amino acid, we have an amino group and a carboxylic group**,** the amino group is the basic one, the carboxylic group is the acidic one. **If the pH of the solution is higher** than the pKa of the material, the acidic group is more capable and has the capacity of donating its proton to the solution more, while **at lower pH values**, the material will be supplied with protons from the solution.

ACCORDINGLY: each carboxylic group in the backbone has a certain pka value which we call it pk1, and each amino group in each amino acid in the backbone has a certain pka value which we call it pk2 and sometimes, the R group has a pKa value.

- The pk1 for carboxylic group is around 2
- The pk2 for amino group in the backbone is around 9.

- There is a concept in the amino acids (related to its titration) called the **isoelectric point**.

- what do we mean by isoelectric points? It is the PH VALUE, where the electricity will be iso " equal " which means that the net charge on the amino acid is zero

Amino Acid	Abbreviation		pK_1	pK_2	pK_R	pI
	3-Letters	1-Letter	-COOH	$-NH_3^+$	R group	
Alanine	Ala	A	2.34	9.69	-	6.00
Arginine	Arg	R	2.17	9.04	12.48	10.76
Asparagine	Asn	N	2.02	8.80	-	5.41
Aspartic Acid	Asp	D	1.88	9.60	3.65	2.77
Cysteine	Cys	C	1.96	10.128	8.18	5.07
Glutamic Acid	Glu	E	2.19	9.67	4.25	3.22
Glutamine	Gln	Q	2.17	9.13	-	5.65
Glycine	Gly	G	2.34	9.60	-	5.97
Histidine	His	H	1.82	9.17	6.00	7.59
Isoleucine	Ile	I	2.36	9.60	-	6.02
Leucine	Leu	L	2.36	9.60	-	5.98
Lysine	Lys	K	2.18	8.95	10.53	9.74
Methionine	Met	M	2.28	9.21	-	5.74
Phenylalanine	Phe	F	1.83	9.13	-	5.48
Proline	Pro	P	1.99	10.60	-	6.30
Serine	Ser	S	2.21	9.15	-	5.58
Threonine	Thr	T	2.09	9.10	-	5.60
Tryptophan	Trp	W	2.83	9.39	-	5.89
Tyrosine	Tyr	Y	2.20	9.11	10.07	5.66
Valine	Val	V	2.32	9.62	-	5.96

From Lehninger Principle of Biochemistry.

** we call the amino acid when the total net charge on it equals zero : **the zwitterion form** and **it is written as ZW**

- How do we can calculate this **zwitterion form**?

By calculating (pk1 +pk2)/2

So here we assume p k1=2 , pk2=9 . So, (2+9)/2

11/2= 5.5 | ⟶ at 5.5 we assume most of the amino acids to be neutrally charged

** that applies to 5-15 amino acids out of 20.

- What other amino acids will have a different value ?
  - The ones which can donate a proton that has a dissociable group of proton on its side chain, (the side chain can participate in proton donation) which applies to the five amino acids that are charged.
    we have 2 amino acids with a carboxylic group in its side chain, 3 amino acids which have an amino group in its side chain, those are the charged ones where each one has a specific pka for the sociable group in its side chain, also we have :

- cysteine (we've discussed before) can donate a proton because it has **SH**.

- selenocysteine can donate a proton because it has **HSe.**

- Tyrosine can donate a proton because it has a hydroxyl group OH-.

We don't have to memorize the no. Of these amino acids, but know that:

- **the acidic amino acids donate their proton in their side chain, at an acidic value below 7 which is around (4 or 4.5)**

- **the basic ones donate their proton at a value higher than 7 (around 8-12)**

  - Exception: histidine, which has a PKa value exactly 6 that (we should memorize) and because it has the PKa value of 6 in its side chain, which is close to the physiological PH, this is why in most active sites of enzymes we will find histidine there.

Now, how to calculate the PKa values for the isoelectric point for those charged amino acids?

- In acidic amino acids, you'll take the two pk values of the acidic amino acid if you have three pk values for example,

take the PK1 value and PK3 (PKa of the acidic side chains) -disregarding the amino group value- add them then divide by 2.

for example, in aspartic acid, the pk1 for the R group in the backbone =1.88
The pk3 of carboxylic group = 3.65
So, we add (1.88+3.65)/2 =2.77
*in the case of basic amino acids, we add the pk of both amino groups then dividing by 2
in tyrosine for example: (10.07+2.20)/2=5.66
we will know the pH value at which it will reach its Zwitterion form

Is it the same in proteins?

Dissociating Group	pK_a Range
α-Carboxyl	3.5-4.0
Non-α COOH of Asp or Glu	4.0-4.8
Imidazole of His	6.5-7.4
SH of Cys	8.5-9.0
OH of Tyr	9.5-10.5
α-Amino	8.0-9.0
e-Amino of Lys	9.8-10.4
Guanidinium of Arg	~12.0

- the values for the free amino acids are a little bit different because the pka changes according to the environment surrounding them. The table is just for you to know variation for these PKA values.

Post translational modification of amino acids

(occurring when they are in residues -proteins- or when they are free and it implies changing in functions)

includes:

-hydroxylation(-OH)

-Carboxylation(-COOH)

-Methylation(-CH3)

-Formylation(-CH=O)

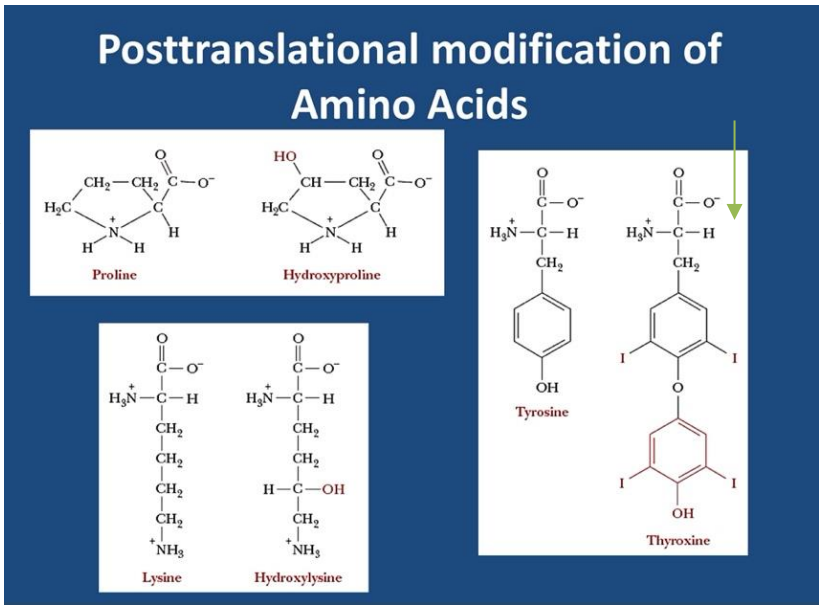
-Acetylation(-CH3CO)

-Prenylation (a farnesyl -contains 15 carbons- or a geranylgeranyl -contains 20 Carbons-)

-Phosphorylation(-PO3-2)

These modifications significantly extend the biologic diversity of proteins by altering their solubility, stability, catalytic activity, and interaction with other proteins.

Here, proline can be hydroxylated to hydroxyproline



Note: **what makes collagen helical is the presence of hydroxyproline.**
Collagen fibers can also be cross-linked

this cross linking is a covalent bond which is present due to the presence of what we call hydroxylysine

The modification in tyrosine is **the addition of another phenyl group (benzene ring)** that has an OH group. **Then a modification occurs with iodine**, if it has 3 iodines then it is called T3 hormone with 4 iodines is T4 hormone (thyroxine). **both T3 & T4 are products of tyrosine**

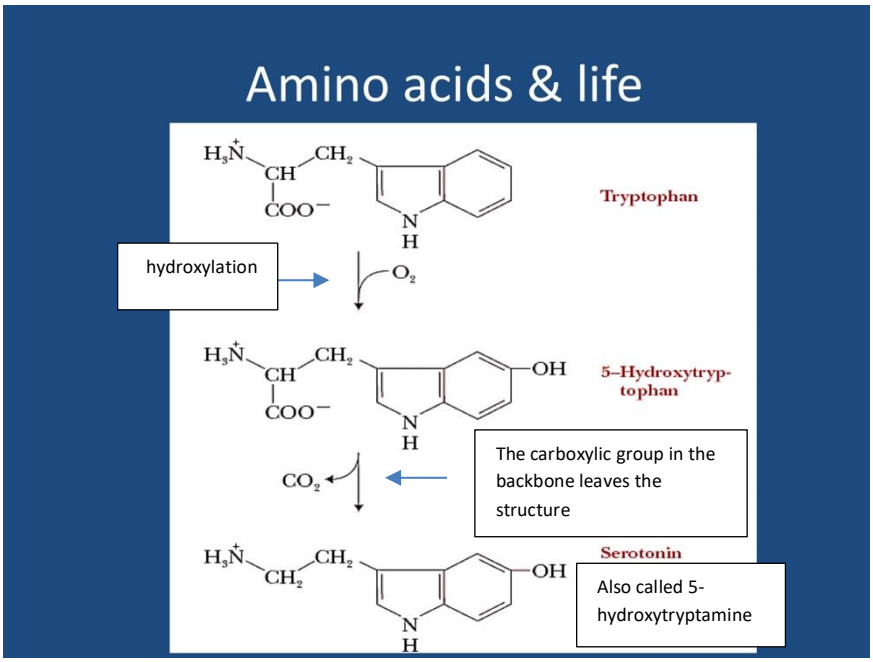
hydroxyproline and hydroxylysine are present in collagen, and both amino acids are modified by an enzyme known as **prolyl hydroxylase, Lysyl hydroxylase** .These enzymes need **vitamin C** to work to function properly. When this enzyme is deficient or defective, or when vitamin C is in shortage, collagen will be disturbed in its structure and this result in a disease called **scurvy** (الاسقربوط)

Amino acids & life:

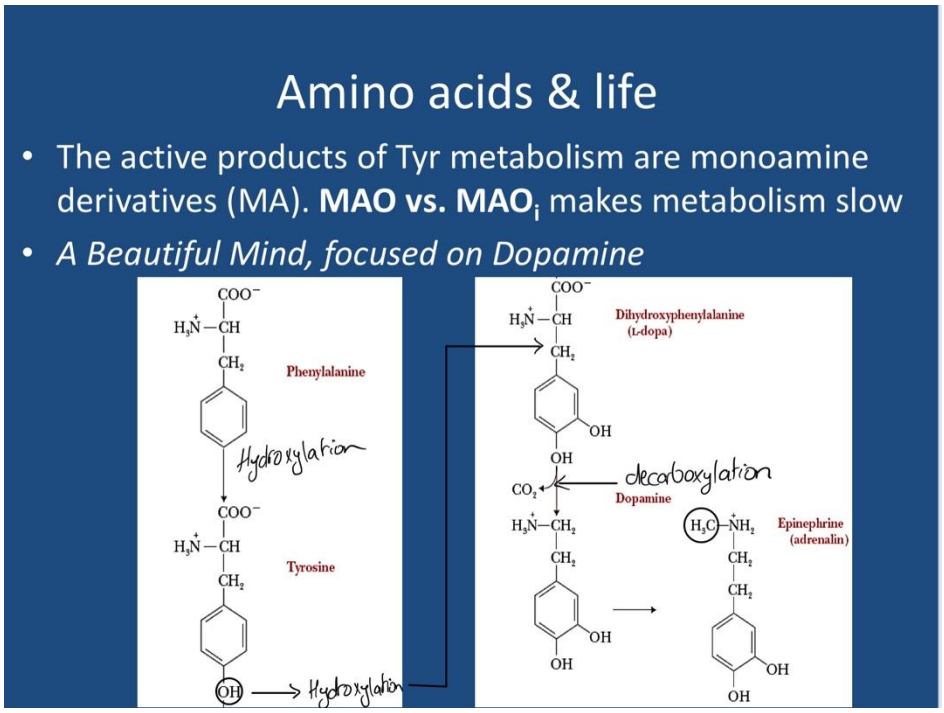
-two amino acids deserve special attention (**Tyr & Trp**) with respect to neurotransmission.

-**Tryptophan is converted to 5 hydroxy tryptophan then via a decarboxylation reaction is converted to 5-hydroxytryptamine (serotonin, sedative effect)**

-Tryptophan is present in **milk causing sleepiness.**

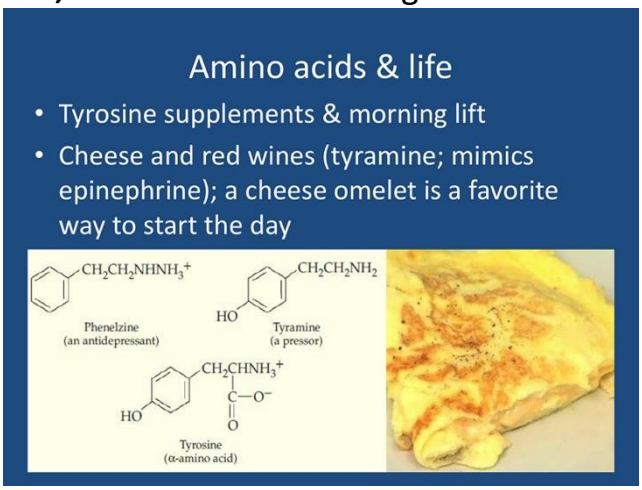


- When serotonin is low its associated with depression and when its high it comes with the manic state (mania)



- Phenylalanine can be hydroxylated therefore producing Tyrosine. Then, Tyrosine is hydroxylated therefore forming Dihydroxy-phenylalanine (L-DOPA) which is decarboxylated (removal of CO2 from the backbone) thus forming Dopamine which through methylation reaction is converted to Epinephrine (Adrenaline) which can be demethylated thus forming Norepinephrine (Noradrenaline).

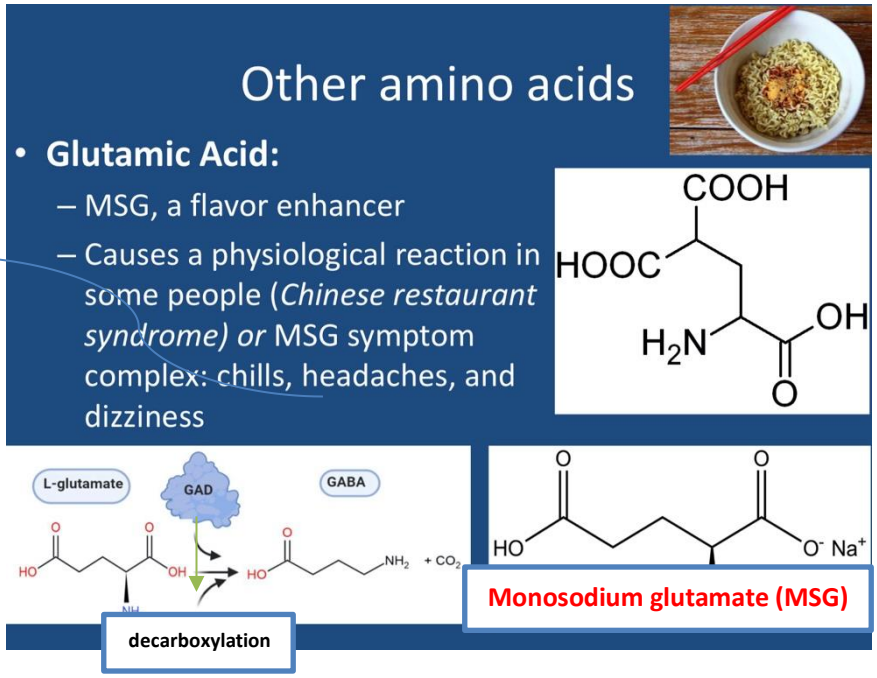
- All the previously mentioned molecules are broken down through an enzyme known as **monoamine oxidase** because all these structures have one amino group hence being known as **monoamines**.
  Clinical application:-in depression the patient is given monoamine oxidase inhibitors (MOAi) thus preventing the breaking down of monoamines leading to an **increase in the concentration of adrenaline, noradrenaline** which gives an active state to that person.



- Cheese and red wines have a molecule known as **tyramine** which is very close in its structure to tyrosine, it implies the same function, mimicking epinephrine in its action. This explains the morning lift you get when eating breakfast.

γ- aminobutyric acid inhibitory neurotransmitter

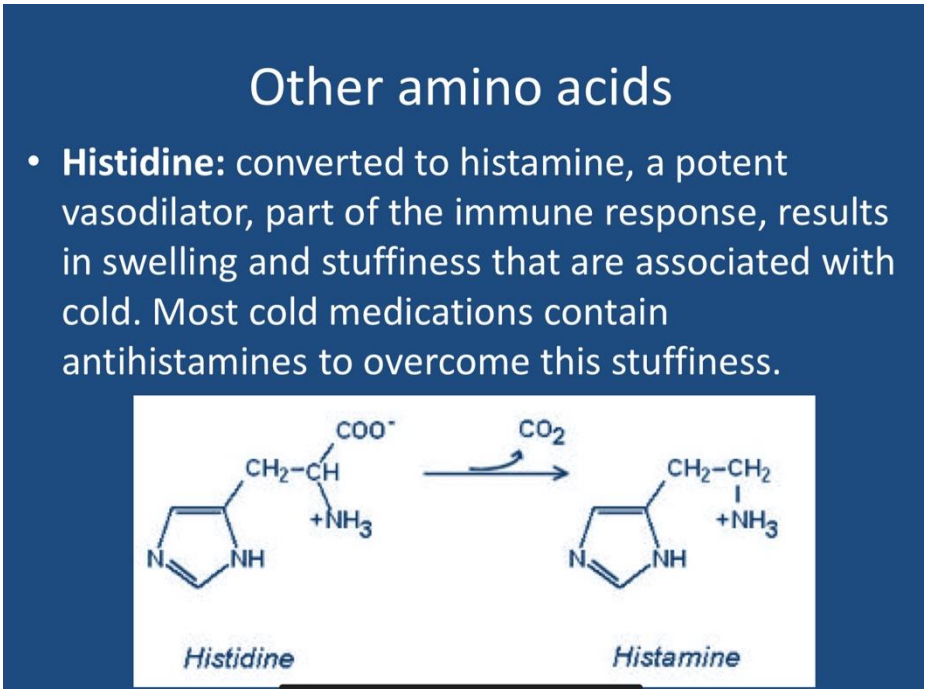
The side chain includes a carboxylic group



- **MSG** is a flavor enhancer with the 5th taste (the 4 main tastes are: sour, bitter, sweet and savory) called the **umami taste,** which is meaty and adds sharpness and depth , it is used as a flavor enhancer in many dishes especially in Chinese restaurants, however it can cause certain reactions like **headaches, chills and dizziness** therefore it's **called Chinese syndrome or MSG symptom complex.**

- **Glutamic acid** can be converted into **γ-carboxyglutamate** via a carboxylation reaction. In **γ-carboxyglutamate, Gamma carbon is attached to 2 carboxylic groups** (2 negative charges) in its side chain and is found in proteins (**Clotting factors**) responsible for blood clotting (The presence of the 2 negative charges enables its binding to Calcium thus attracting more platelets, this process is facilitated by the use of **vitamin.** Thus, vitamin K deficiency is associated with bleeding.

- **L-Glutamic acid (Glutamate)** can be converted to a **inhibitory neurotransmitter** known as **Gama-Aminobutyric acid (GABA)** via a decarboxylation reaction (removal of CO2 from the backbone) catalyzed by an enzyme known as **Glutamate decarboxylase (GAD).**



- **Histidine** ,through a decarboxylation reaction, is converted into **histamine** which acts as a potent vasodilator, Bronchoconstrictor, part of the immune response (Allergic reactions) , which results in redness spasms in vocal cords and vessels as well as swelling and stuffiness(These two symptoms are associated with cold). Treating cold and allergies involves the use of **Antihistamines** to overcome this stuffiness. Recall that **Histamine** is a product of **Mast cells and basophils.**

The End