Lecture : ....2........

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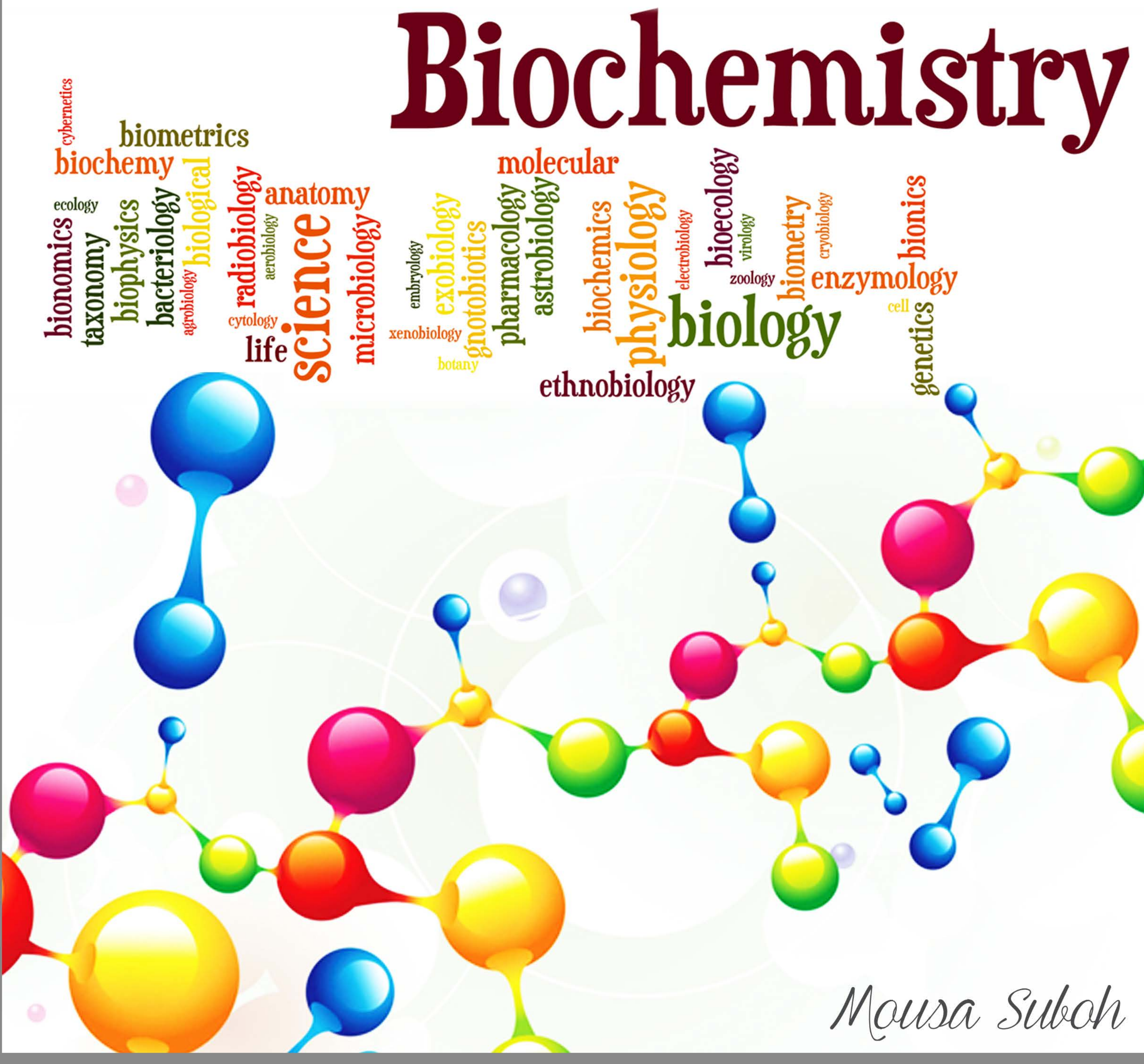
Medical Committee
The University of Jordan



Lecture 2 Dr. Nafith AbuTarboush

-We have 20 essential Amino Acids, all of them are chiral except for Glycine

-These 20 Amino Acids can be subdivided into 3 categories:

A- Polar amino acids: the side chain (R group) contains polar (hydrophilic) parts so it can forms Hydrogen bonds with H2O. In those amino acids R may contain:

1-OH group: as in Serine, Threonine and Tyrosine

2-SH group: as in Cysteine

3-Amide group: as in Glutamine and Asparagine

4-NH2 or Nitrogen act as base (basic amino acid): as in Lysine Arginine and Histidine

5- COOH (acidic amino acids): as Aspartic and Glutamic acids.

B- Non polar amino acids: R is alkyl hydrophobic group which can't enter in hydrogen bond formation. 9 amino acids are non polar:

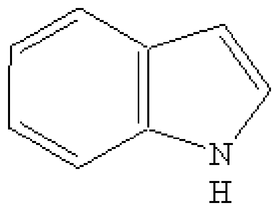
1- Glycine, it is achiral

2- Alanine has a methyl group in the side chain.

3- Valine is branched amino acid in the side chain, same story for Leucine and IsoLeucine.

4- Phenylalanine has a benzene ring

5- Tryptophan is the largest one, it has two cycles, it has the



indole ring Indole

6- Proline has a secondary N, the Nitrogen in the backbone is attached from both sides by the alpha carbon and by carbons from the side chain.

7-Methionine has a sulfur atom in the side chain, so it's not reactive, it can't engage in the reactions, except if it's subjected to a very high oxidizing agent. Methionine can be oxidized but it needs a very powerful oxidizing agent, usually it's not reactive, why? Because the sulfur is attached from both sides with carbons.

Non-polar	Polar	Charged (positive)	Charged (negative)
Alanine	Serine	Lysine	Glutamate
Valine	Threoeine	Arginine	Aspartate
Leucine	Glutamine	Histidine	
Isoleucine	Asparagine		
Mehionine	Cysteine		
Tryptophan	Tyrosine		
Phenylalanine			
Proline			
Glycine			

Usually the backbone of the amino acid is engaged in the hydrogen bonding. Nitrogen serves as a donor for H+ and the carboxyl group serves as an acceptor for that H+. In case of

Proline, it cannot serve for hydrogen bonding with its nitrogen, because the nitrogen is engaged in both sides with carbons.

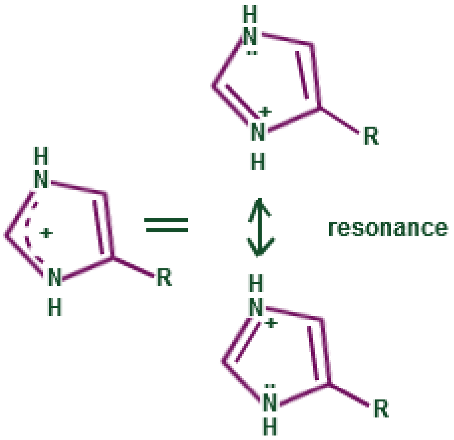
Phenylalanine is a non polar amino acid with a benzene ring in its side chain. The indole ring is present in the Tryptophan and it's the largest amino acid. Asparagine has an amine group and it shows resonance, same story with Glutamine. Serine is a polar amino acid with a hydroxyl group in its side chain and one carbon atom in the side chain, when Serine compared with Alanine we will find that they have the same structure except for the addition of hydroxyl group, this is why during metabolism we can converge Alanine to Serine and Serine to Alanine by the addition of hydroxyl group or removal of that group. Threonine can be converted to Valine.

Glutamic acid and Aspartic acid are negatively charged amino acids. Tyrosine is a polar amino acid.

Cystine has a free –SH group (thiol group) which is reactive and Cystine can lose the Hydrogen by oxidation reaction, so when we oxidize the cystine or any other molecule H+ will be lost. If we have 2 Cystine and each one lost its H+, and S from each Cystine can be engaged in what is called disulfide bridge or bond, and it's very important in preserving the protein structure not how the folding in the protein occurs, so the protein can save its structure by disulfide bridge, eg; antibodies and insulin which has a structure that is preserved by the disulfide bond.

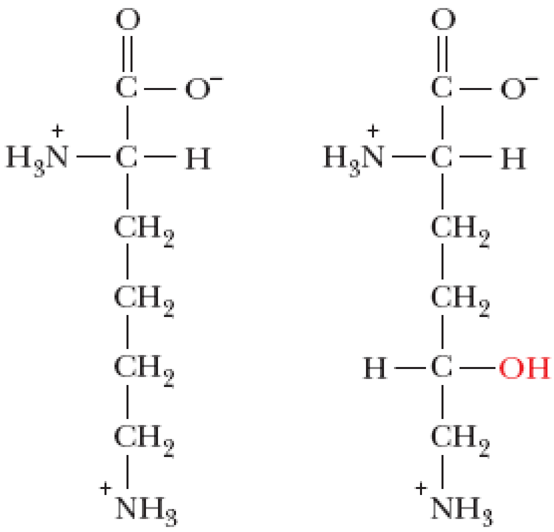
Lysine basic amino acid with an amine group in the side chain, and Arginine with a guanidine group in the side chain, and it can be used in forming the plastics and explosives.

Histidine has an imidazole ring and it shows resonance.



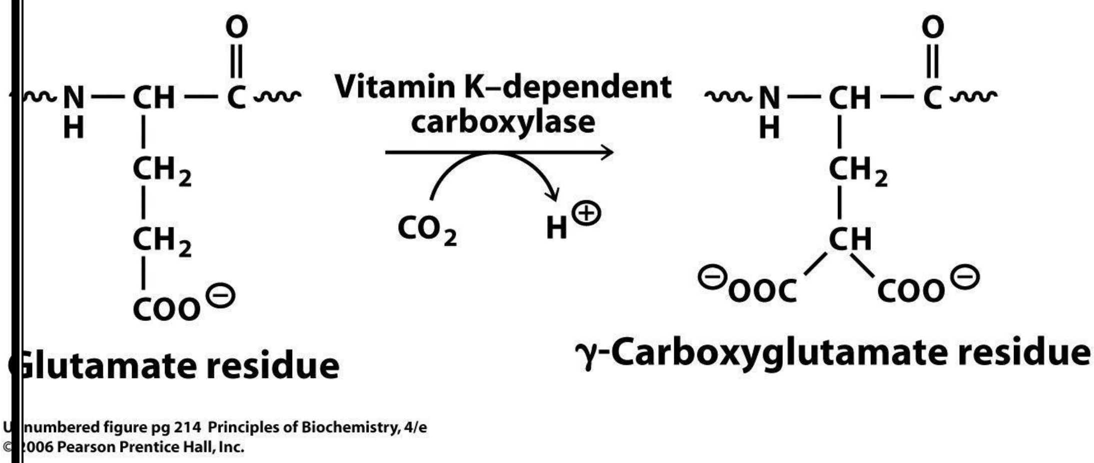
Amino acids are available in markets either everyone alone or as a mixture that used by the athletics.

Modification on the amino acids may occur in the human body. As an example, lysine and proline in collagen, post transitional modification of lysine and proline, hydroxylation occurs and cause bridging inbetween lysines and prolines to produce stronger collagen. Without this hydroxylation there is no bridging and as a result there will be week collagen, expressed in a disease called Scurvy.

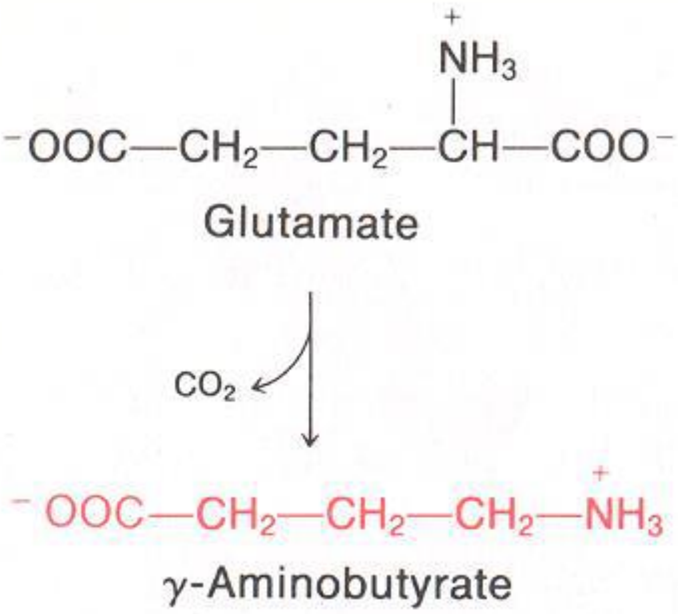


Lysine Hydroxylysine

In Glutamate, more than one modification can be applied on this amino acid, like Gamma carboxyglutamate, what does that mean? we should go back to the naming of the carbons, Alpha carbon is found in amino acid attached to carboxylic and amine groups and R group (side chain), the carbons of side chain are Beta and Gamma, on the Gamma carbon, called Gamma carboxyglutamate, so on the Gama carbon there is a carboxylic group added to this glutamate, and now it's a clotting factor, so Gamma carboxyglutamate is a clotting factor, to be active, it is necessary to have a post transitional modification to the glutamate on the Gamma carbon and addition of carboxylate, Vitamin K is essential for the process



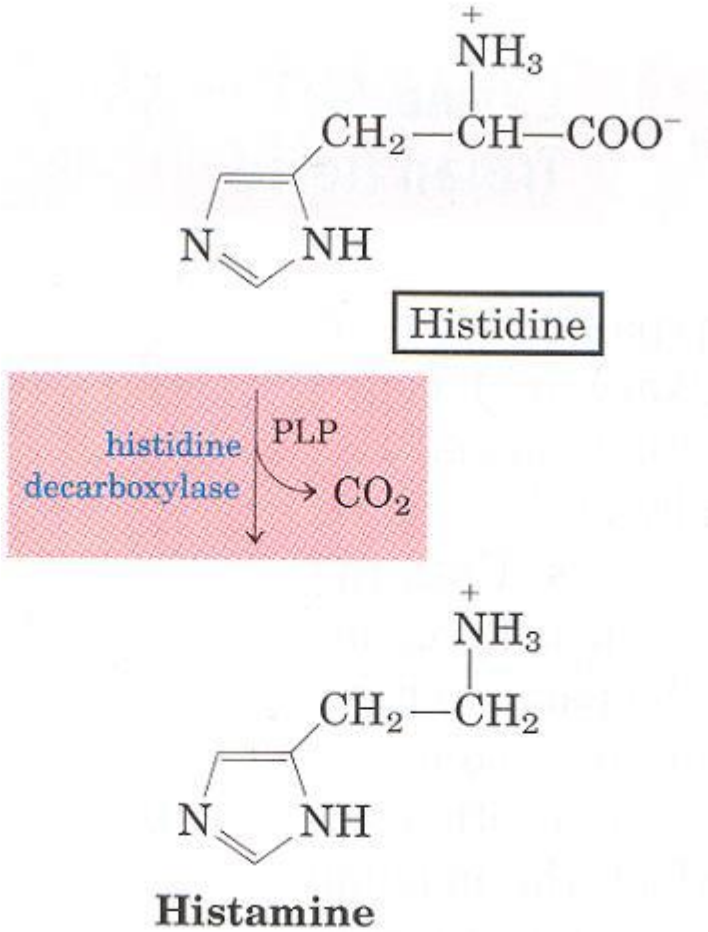
-when we add a carboxylic group to glutamate, clotting of blood happens, but when we remove the carboxylic group of the back bone from the same glutamate by a decarboxylation reaction we will have what we call g-aminobutyric acid (GABA) which is an inhibitory neurotransmitter in (CNS).



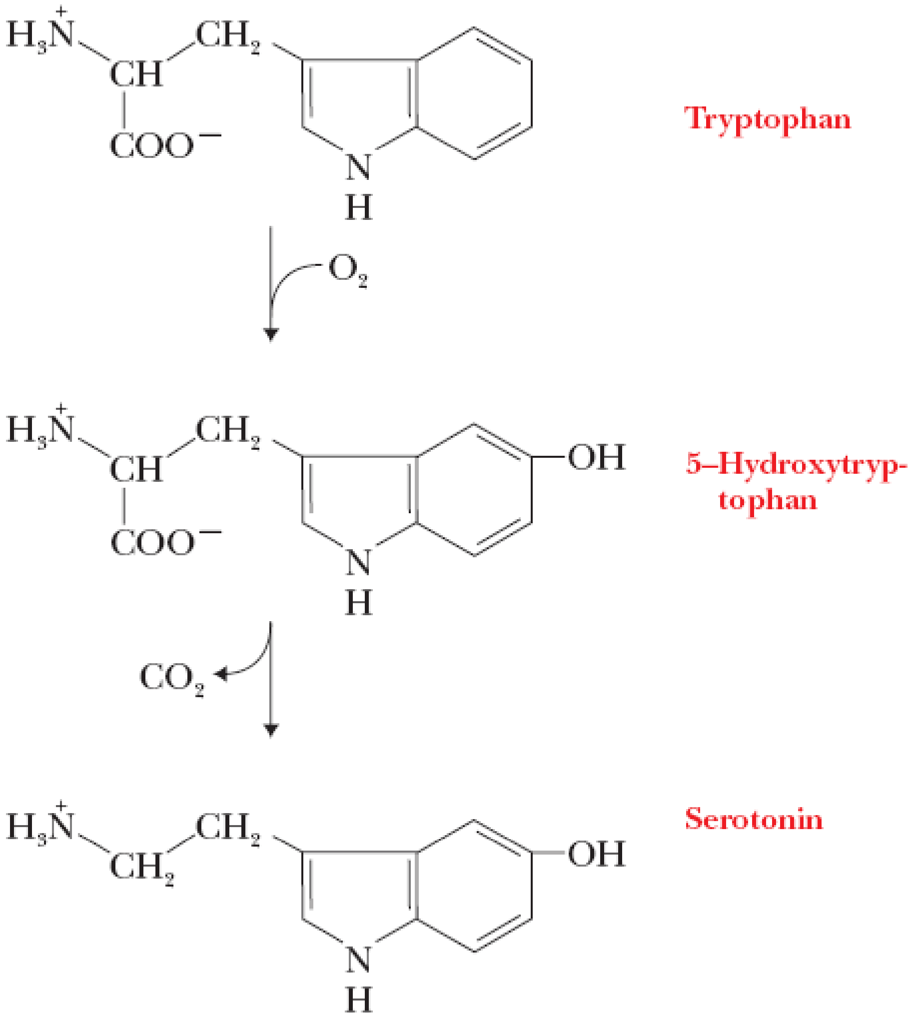
There is another modification of glutamate when sodium added called monosodium glutamate (MSG), it is a flavoring agent used in chinese restaurants. With some people it may show some side effects such as chills, headaches, and dizziness. They call this disease Chinese restaurant syndrome.

- Histidine which has the imidazole ring, when the carboxylic group which is found in the backbone of the amino acid is detached by decarboxylation reaction, Histamine will be formed. Histamine increases the allergic reactions by increasing the blood in the inflamed area, it's responsible for the symptoms of the inflammation, like redness and swelling in the inflamed area and Contributes to inflammatory response, and causes constriction of smooth muscles in respiratory system, so that when patient has influenza we will give him Anti histamine.

Histidne is changed to Histamine by Histidine decarboxylaze in decarboxylation reaction.

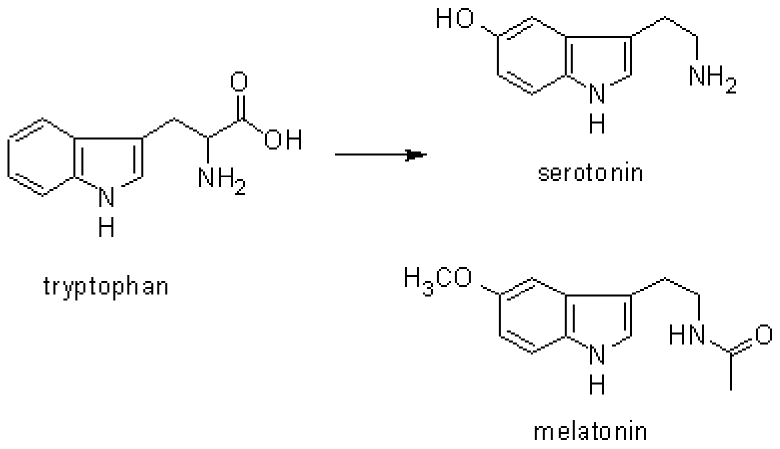


Tryptophan is the largest amino acid which has indole ring in its side chain. Tryptophan will be converted to 5-hydroxytryptophan by hydroxylation reaction, hydroxyl group will be added to the carbon atom number five in the indole ring. When we remove the carboxylic group, it will be called 5-hydroxytryptamine which is the serotonin, sedative NT. When serotonin is relatively high, the patient will suffer from mania, and when it's relatively low, patient will suffer from depression.



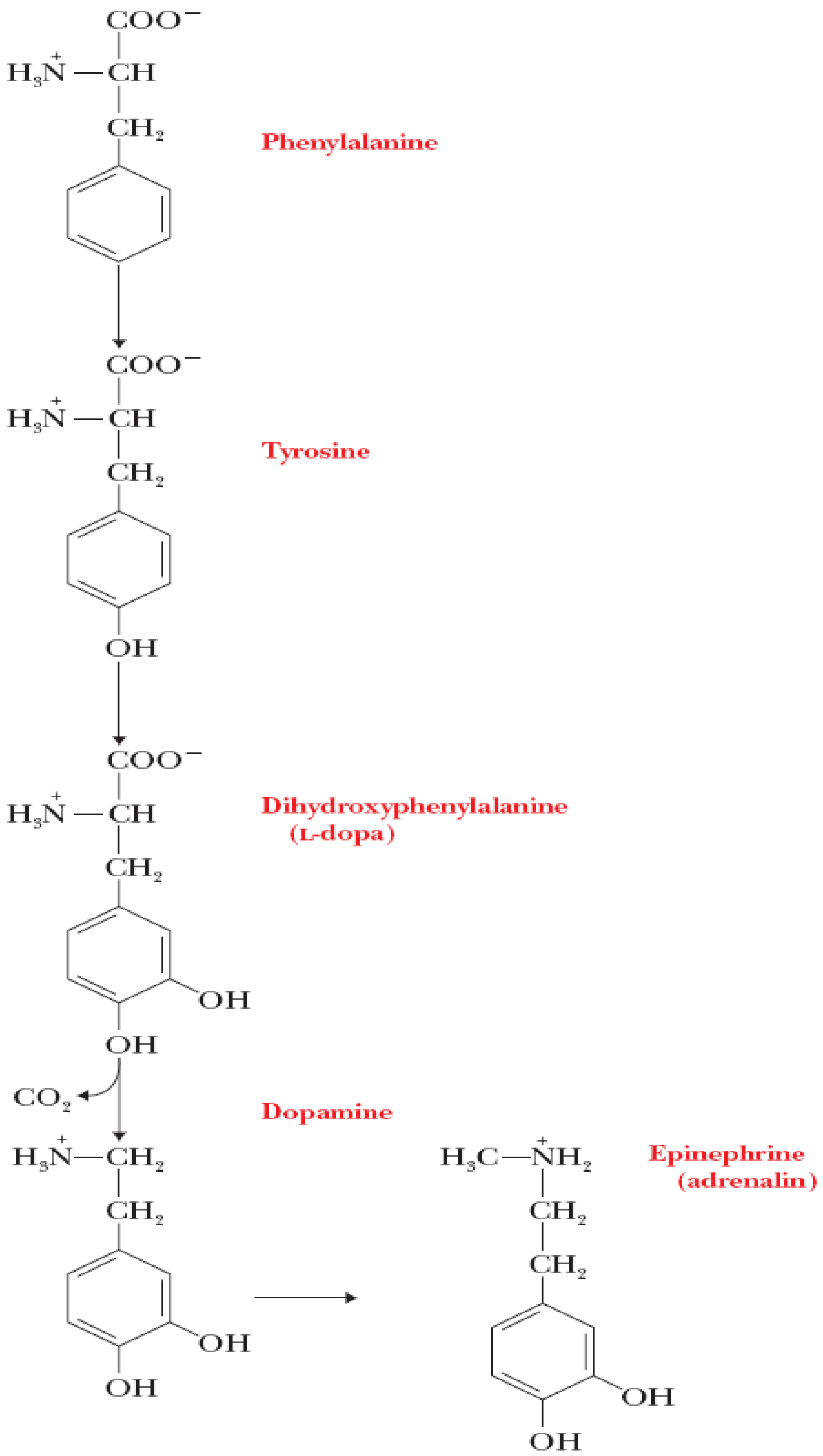
Milk contains high amounts of Tryptophan, so when we drink milk Tryptophan will be converted to serotonin, and it makes the person restful.

Melatonin is a hormone responsible for our biological clock (day and night cycle). Melatonin is available commercially and it's derived from Tryptophan.



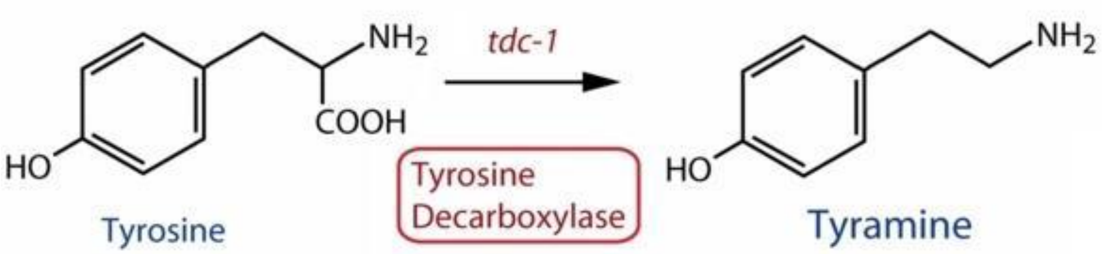
Tyrosine and Tryptophan have a special interest in the CNS, they give us a lot of NT.

Tyrosine can be produced by the addition of OH (hydroxyl group) to Phenylalanine by the enzyme Phenylalanine hydoxylase, then another hydroxylation reaction will produce L-Dopa and the L-Dopa will be converted to dopamine, then dopamine will be converted to epinephrine and norepinephrine, all these NT are derivatives of Tyrosine and called catechol amines because they have catechol ring in their structure, and the catechol is benzene ring has two hydroxyl groups.



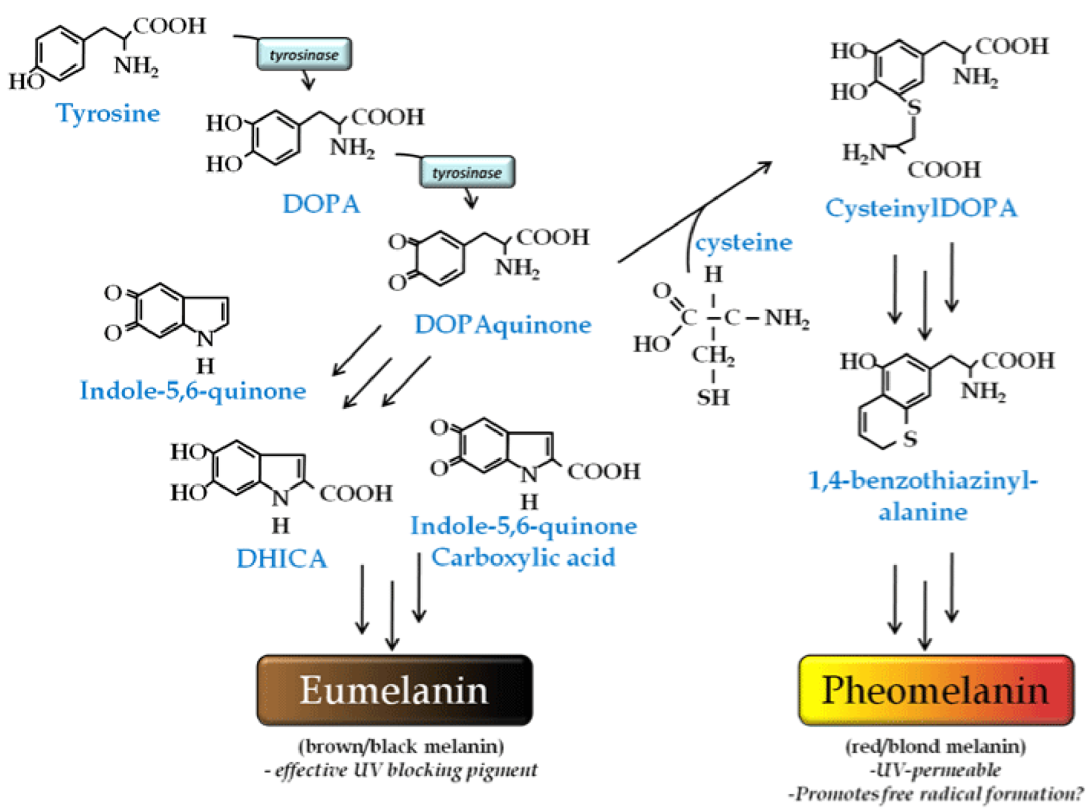
Monoamines are derivatives of Tyrosine (catechol amines are monoamines) they can be produced by enzymes, each enzyme play a role in the cycle, and each enzyme is called momamine oxidaze. Momoamine oxideases break down the catechol amines (if you have epinephrine for example, it'll be broken down by these monoamine oxideases. Same story for norepinephrine, dopamine and L-Dopa). When they're broken down they'll be inactive. When you give a patient monoamine oxidizing inhibitor (MAO inhibitor) you will inhibit these enzymes and increase the number of epinephrine and norepinephrine and thus the patient will be excited. We use these inhibitors with patients who suffer from depression.

Tyramine is another derivative of Tyrosine by decarboxylation reaction, the carboxylic group which is found in the backbone will be detached and thus Tyrosine will be converted to Tyramine (Tyramine is similar to epinephrine). Tyramine which mimics the action of epinephrine is numerous in cheese so that many people eat cheese in the morning to start their day.



Thyroxine (T4) is another derivative from the Tyrosine, it has the same structure of Tyrosine but with another benzene ring which has hydroxyl group and iodine groups.

Melanin is also derived from Tyrosine which is responsible for the skin color, through a series of reactions it can give either Eumelanin which is responsible for the black color or Pheomelanin which is responsible for brown color (blonde).

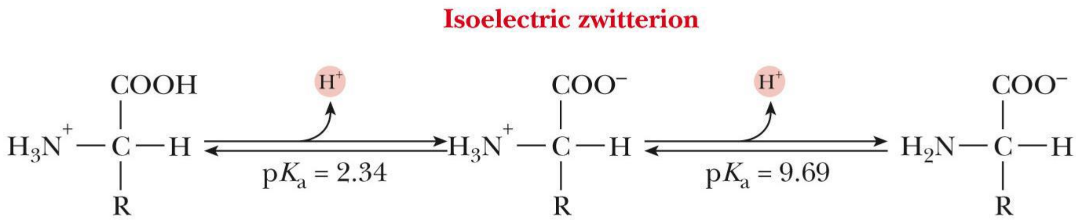


Ionization of amino acids:

There are ionizable groups within amino acids like the carboxyl and amine groups, both have H+ which could be lost. Is the R group an ionizable one? it could be either ionizable or not, depending on the nature of this R group, at physiological pH (7.4) in each amino acid we have at least two ionizable groups, carboxylic group is acidic which means at physiological pH it has been already donated its H+ so its negatively charged, and amine group is basic which means at physiological pH the H+ will be attached to the amine group and it will be lost at high pH.

At very low levels of pH (below 2) the H+ is retained in the carboxylic group and the amine group is already positively charged, when we increase the pH the chance of losing the H+

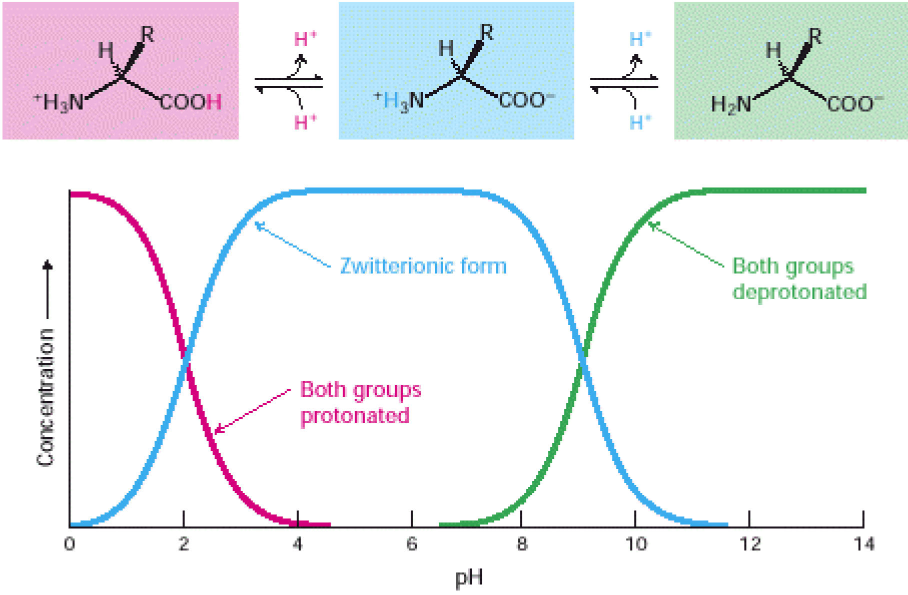
from the carboxyl group will be high because it's an acidic group. When the H+ is detached it leaves the carboxyl group negatively charged then the total charge of this molecule is zero, when total charge (net charge) of the molecule is zero we call it Zwitterion, when the pH is high, now H+ of the amine group will detach and the total charge will be -1. All these steps occur when we deal with only 2 ionizable groups.



Isoelectirc point: it's the point where the molecule has a net charge of zero, Zwitterion molecule. This point is important and it's calculated for single amino acids, short peptides, polypeptides, and even for proteins, to know the techniques of enzymes.

At the image below, both groups -amine and carboxyl groups- are protonated in the red line, and the zwitterion form is in the blue line, and in the green line, both groups are deprotonated.

At low levels of pH, both groups have H+ and a net charge of +1, then H+ in the acidic group will detach and this will increase the chance of having the zwitterions form -the net charge here is zero- then at high levels of pH the amine group will lose its H+ and we will have a net charge of -1.



At which level the carboxyl group will lose its H+?

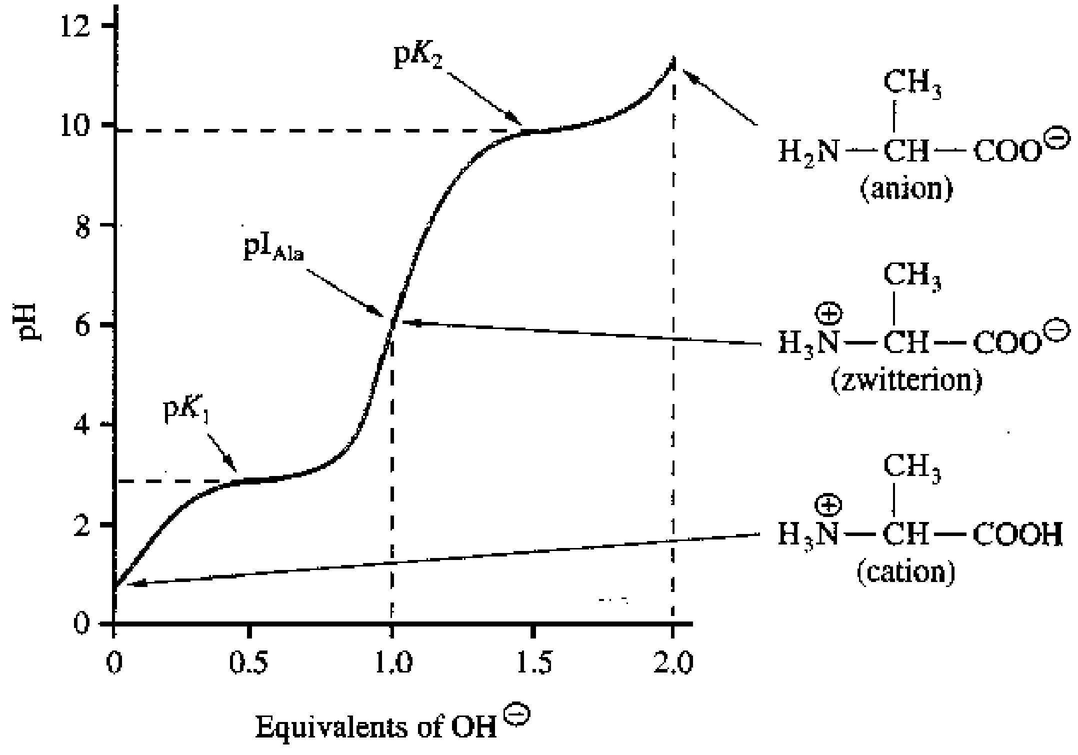
Every amino acid will lose H+ of the carboxylic group at certain pH, which is 2, and the amine group will lose its H+ at level of pH 9.

We took Henderson-Hasselbalch Equation with Dr. Nayef which is pH= pKa + log ([conjugate base] / [weak acid]), we have ionizable groups, carboxyl group in the backbone can lose its H+ and amine group in the backbone can lose the H+ and if we have ionizable group in the side chain it may have a structure that can lose the H+ if it contains oxygen, nitrogen, or sulfur, this situation is found only in polar and charged amino acids. How can we use this equation? We have to know the pKa for every group, pKa for carboxylic group = 2 and amine group = 9. So at certain pH, how much of the carboxyl group will be ionized and not ionized?
Eg: Alanine is not polar amino acid and the side chain is CH3 so it is not ionizable, so it has only two ionizable groups, so at the curve of titration we see expression for two groups, pKa for carboxyl group = 2 and pKa for amine group = 9.

We start to increase the OH- which means that you are increasing the basic components in the solution and as a result the pH will increase. At first, the acidic group (carboxyl group) will lose its H+, then we end up with a zwitterion molecule, then H+ will be lost from the amine group so the total charge now is -1.

How could we know the isoelectric point -pI- for this amino acid and every amino acid that has <u>only</u> two ionizable groups?

pI= (pKa1+pKa2)/2
pI=(9+2)/2 = 5.5



Best of luck