YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 1 - Biochemistry

Lec. Title : Metabolism of Neurotransmitters

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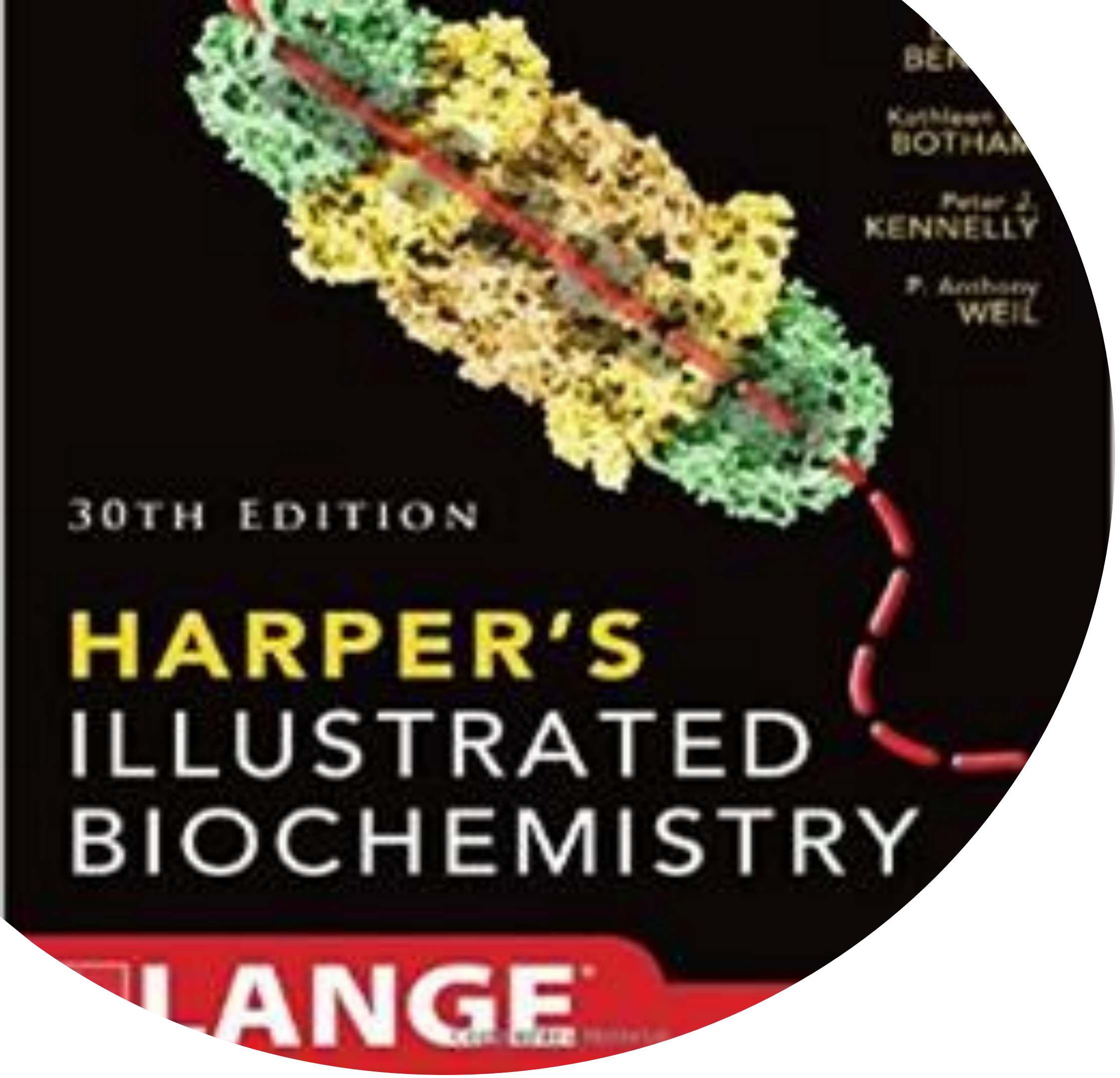


Metabolism of Neurotransmitters

Dr. Mazhar Al Zoubi | CNS-1 Biochem

Note: the green colored notes indicate what the doctor said in the lecture ^-^

Outline

- Discuss the synthesis and degradation of gamma-amino-butyric acid (GABA)
- Discuss the synthesis and degradation of dopamine, epinephrine and nor-epinephrine
- Discuss the formation and catabolism of serotonin
- Discuss the glutamate metabolism. (amino acid which is important in GABA generation)
- Understand the brain peptides as neurotransmitters

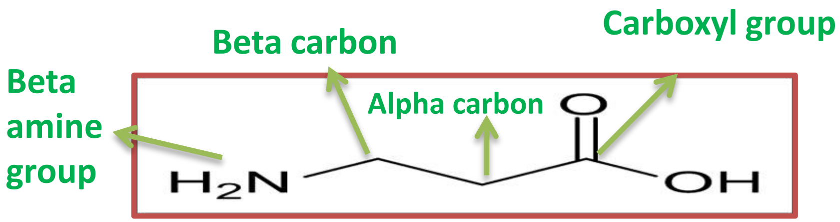
gamma-amino-butyric acid (**GABA**)

- **From recording:**
- **To understand the difference between such kind of amino acids and another amino acids we have to discuss the basic structure of them which consists of a centrally located alpha carbon that attach with:**

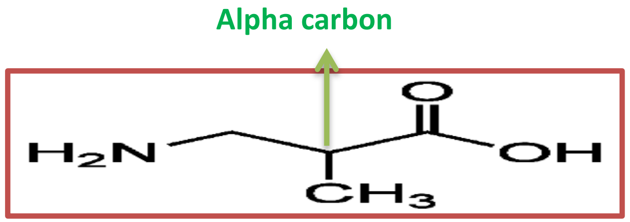
1. **alpha carboxyl group**
2. **alpha amine group**
3. **hydrogen molecule**
4. **side chain (the carbons in this side chain are named beta, gamma etc. regarding to there place relating to alpha carbon)**

- **This type of amino acids is called alpha amino acid , what about non- alpha amino acids??!**

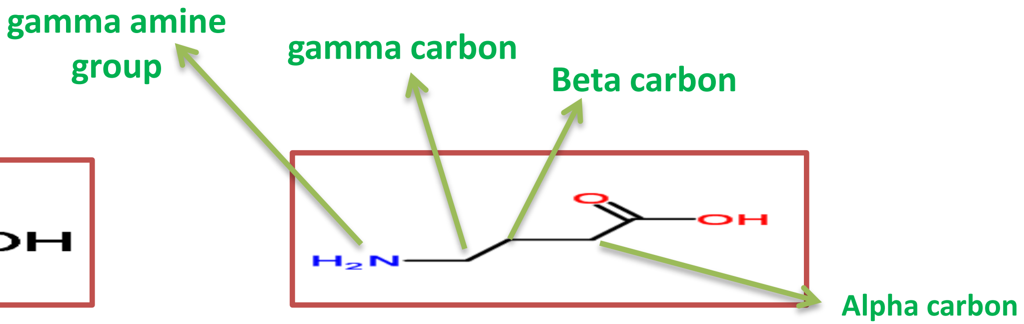
NON-α-AMINO ACIDS:



1. β-alanine



2. β-aminoisobutyrate



3. γ-aminobutyrate (GABA)

Here note that the amine group is named beta amine group because it's attached to beta carbon

The same story ^-^

Here note that the amine group is named gamma amine group because it's attached to gamma carbon

gamma-amino-butyric acid (GABA) cont.

- **Brain inhibitory neurotransmitter** altering transmembrane potential differences

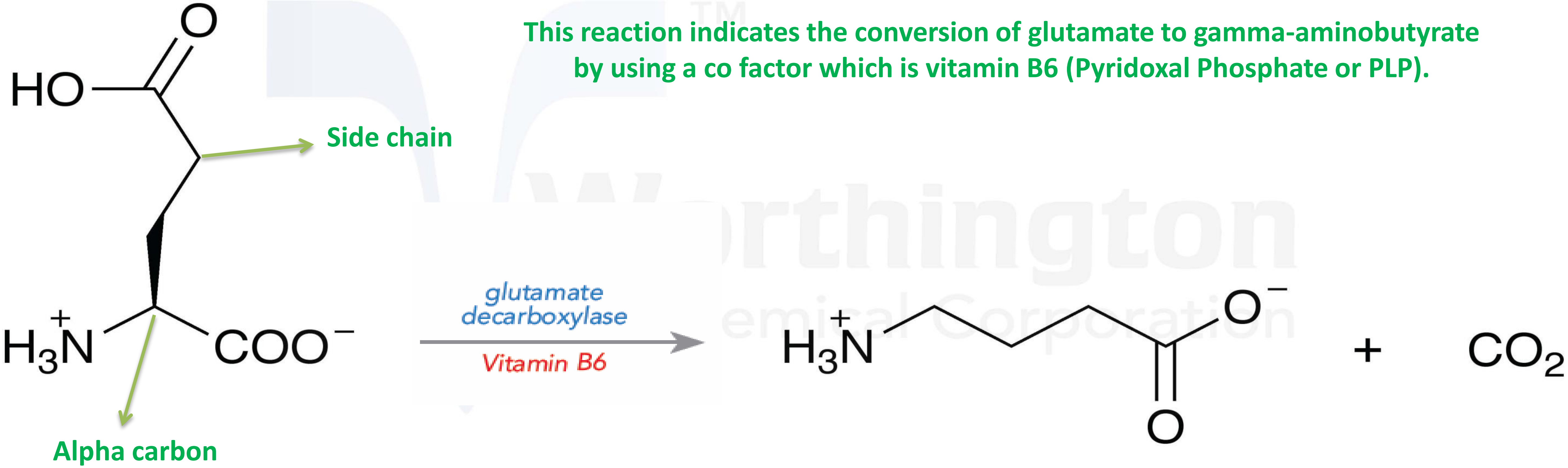
- Formed by decarboxylation of glutamate by L-glutamate decarboxylase

$$^{+}H_3N - CH_2 - CH_2 - CH_2 - COO^{-}$$

γ-Aminobutyrate

Glutamate Decarboxylase

This reaction indicates the conversion of glutamate to gamma-aminobutyrate by using a co factor which is vitamin B6 (Pyridoxal Phosphate or PLP).



L-Glutamic acid

γ-Aminobutyrate

- # From recording:

- **Glutamate is an important amino acid because it gives us an important molecules and can be synthesized from many sources like:**

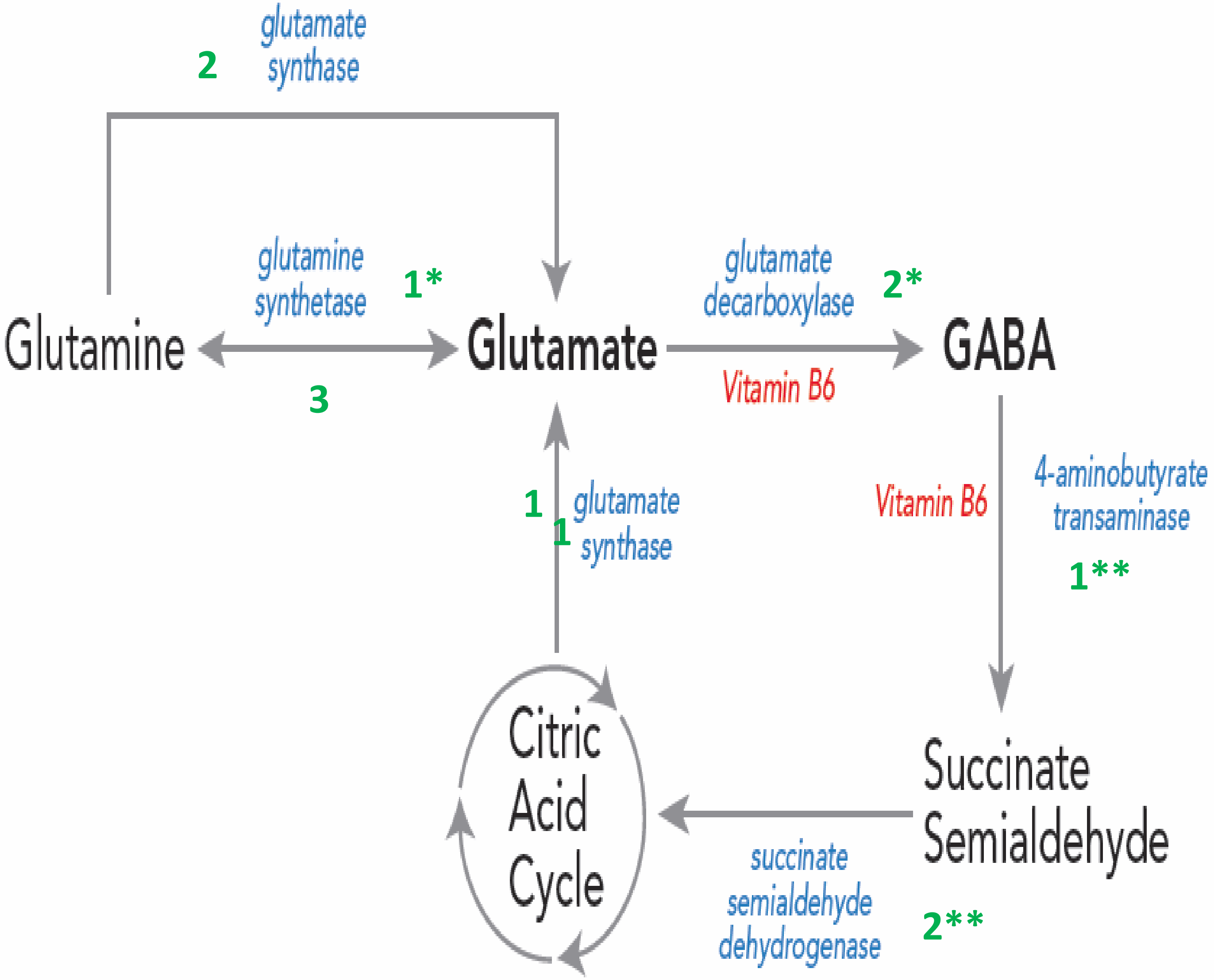
1. **Kreps cycle by glutamate synthase.**
2. **Deamination of glutamine**
3. **transamination reaction**

- **Also it give us a different structures like:**

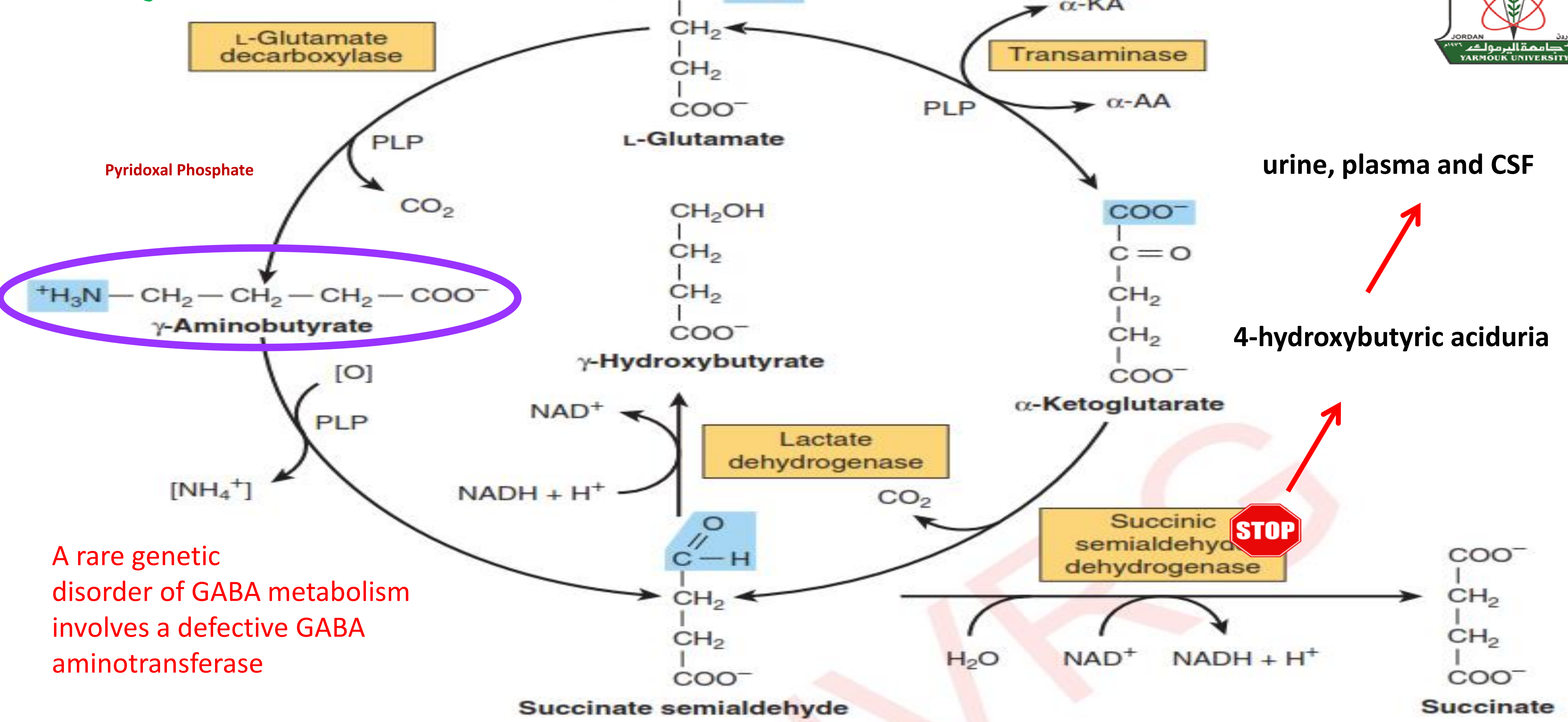
1. ***Glutamine, by glutamine Synthetase enzyme (needs ATP)**
2. ***GABA by glutamate decarboxylase and vitamin B6 .**

- **After GABA formation**

1. ****it catabolized to succinate semialdehyde by 4-aminobutyrate transaminase (transamination reaction).**
2. ****succinate semialdehyde then will be degraded in citric acid cycle**



ما تخافوا من شكل السلايد لإنه الدكتور شرحه
بالتفصيل الممل وإن شاء الله رح يكون سهل



A rare genetic disorder of GABA metabolism involves a defective GABA aminotransferase

FIGURE 30–14 **Metabolism of γ-aminobutyrate.** (α-AA, α-amino acids; α-KA, α-keto acids; PLP, pyridoxal phosphate.)

- As we said one reaction of glutamate is to be converted to GABA by glutamate decarboxylase and PLP (step 1).

- Glutamate also can go a second reaction which is transamination(step 2) to form alpha ketoglutarate, but wait! What is the transamination reaction?!

- It's a reversible reaction involves a conversion of amino acid (glutamate in our story) to ketoacid (alpha ketoglutarate) by donating of it's amine group to another ketoacid (alpha-KA) to be converted to amino acid (alpha-AA)
- So we need a keto acid to be converted to amino acid and amino acid to be converted to keto acid. (two reactions in one reaction)
- Keto acid ⟷ amino acid
- Amino acid ⟷ ketoacid

- Both of them(GABA and alpha ketoglutarate) will be converted to succinate semialdehyde (step 3), GABA will be converted by GABA aminotransferase.

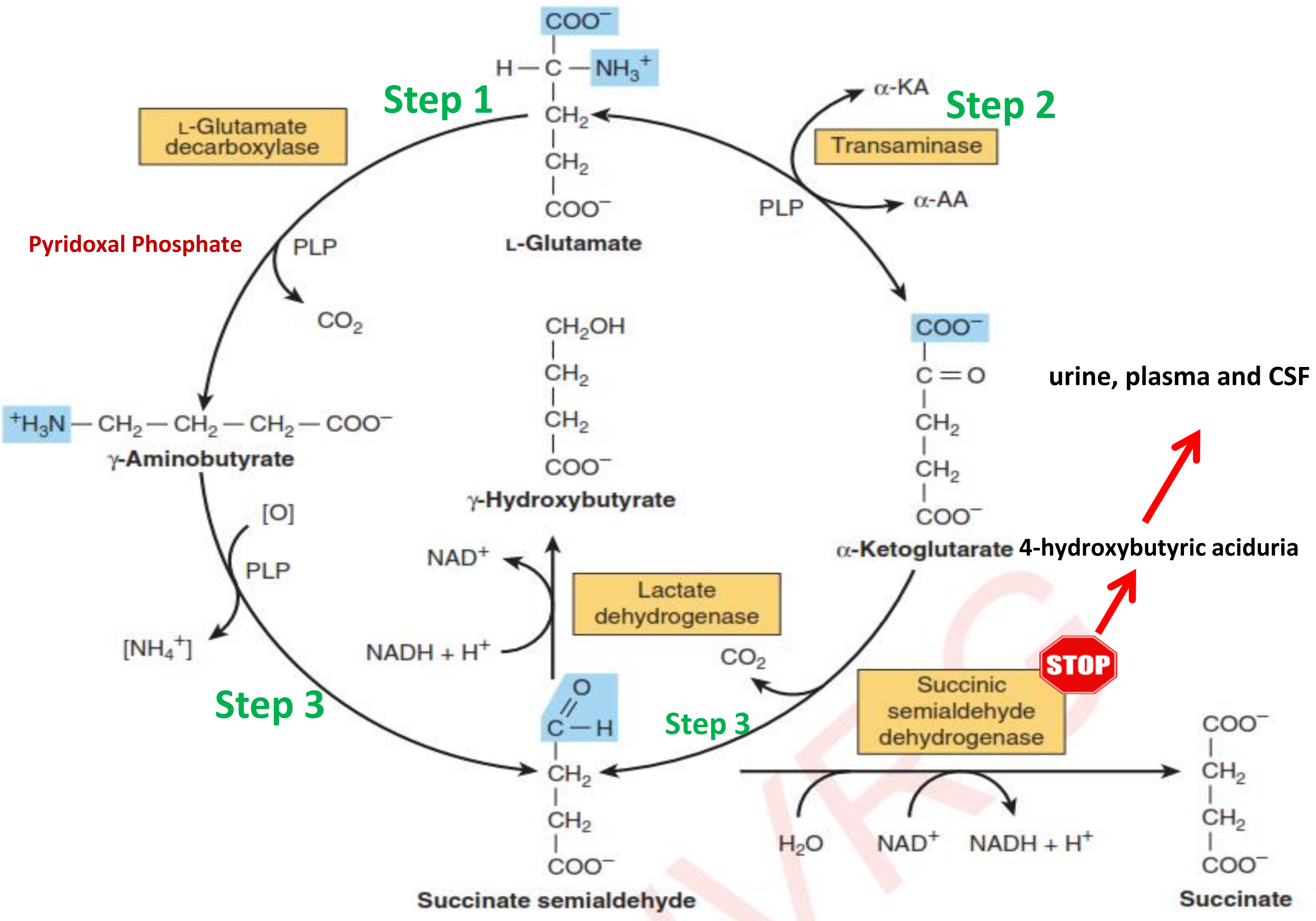


FIGURE 30–14 **Metabolism of γ-aminobutyrate.** (α-AA, α-amino acids; α-KA, α-keto acids; PLP, pyridoxal phosphate.)

A rare genetic disorder of GABA metabolism involves a defective GABA aminotransferase which causes accumulation of GABA and causes neurological disorders

- Now succinate semialdeyde goes two reactions:

1. Conversion to gamma- hydoxybutyrate by lactate dehydrogenase and a reduction factor (NADH) (step 4).

2. Conversion to succinate which is a famous molecule in Kreps cycle as source of energy, that means we can produce energy from glutamate metabolism. This reaction is done by succinic semialdeyde dehydrogenase with oxidizing factor (NAD+) (step 5)

- If this enzyme is inhibited an accumulation of 4-hydroxybutyric aciduria will occur, this molecule will appear in the urine, plasma and CSF leading to neurologic disorders

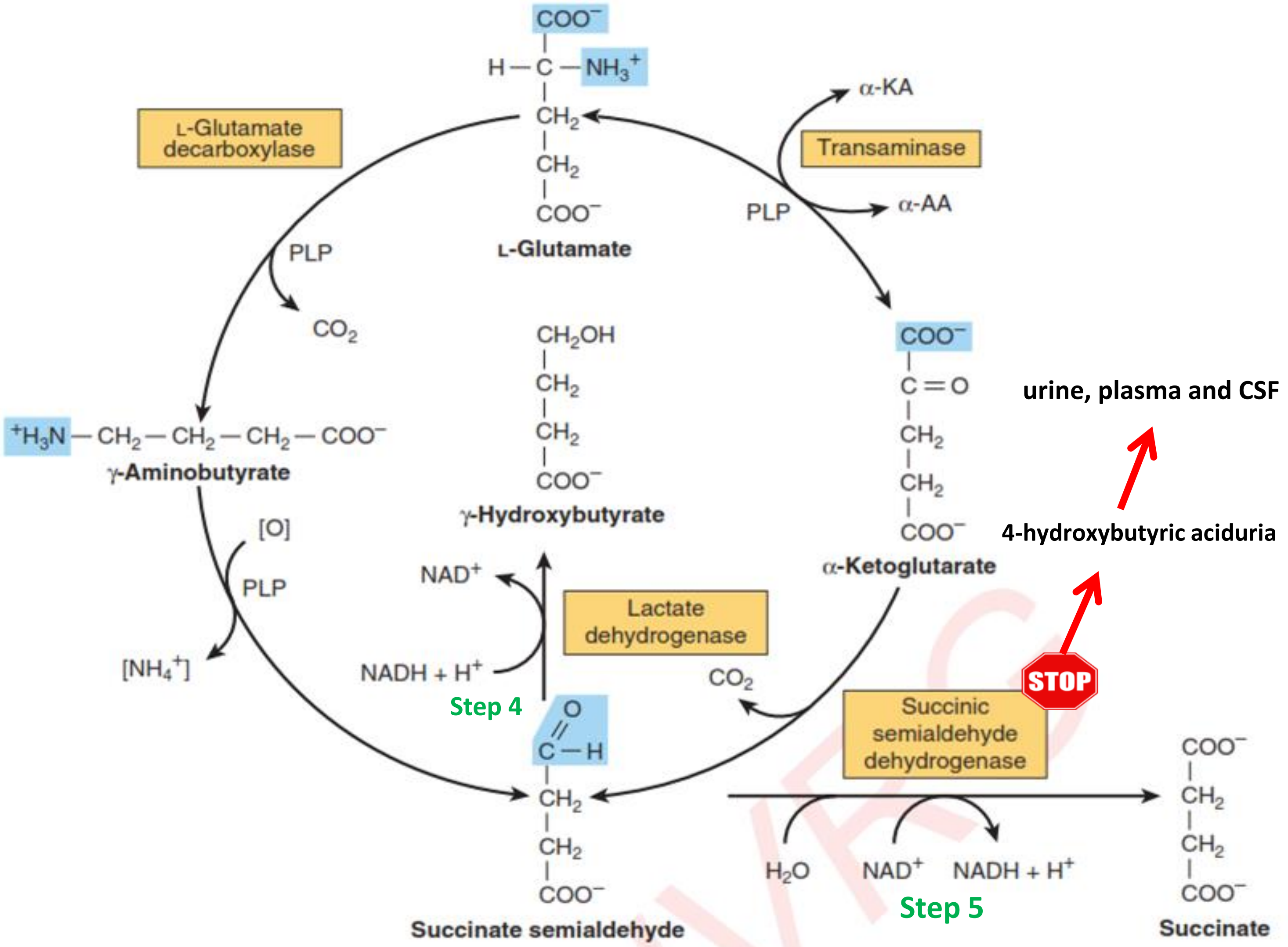


FIGURE 30–14 **Metabolism of γ-aminobutyrate.** (α-AA, α-amino acids; α-KA, α-keto acids; PLP, pyridoxal phosphate.)

Dopamine, Epinephrine and Nor-Epinephrine

- Neural cells convert ***tyrosine*** to **epinephrine and norepinephrine**.
- ***Dopa*** is also an intermediate in the formation of **melanin**, in melanocytes.

- **Epinephrine production is done by four steps:**

1. **Tyrosine hydroxylation**
2. **Dopa decarboxylation**
3. **Dopamine oxidation**
4. **Norepinephrine methylation**

- **You have to know the steps, co factors and enzymes…**
- **The steps are circled by red color , the cofactors by green and enzymes are in the orange boxes.**

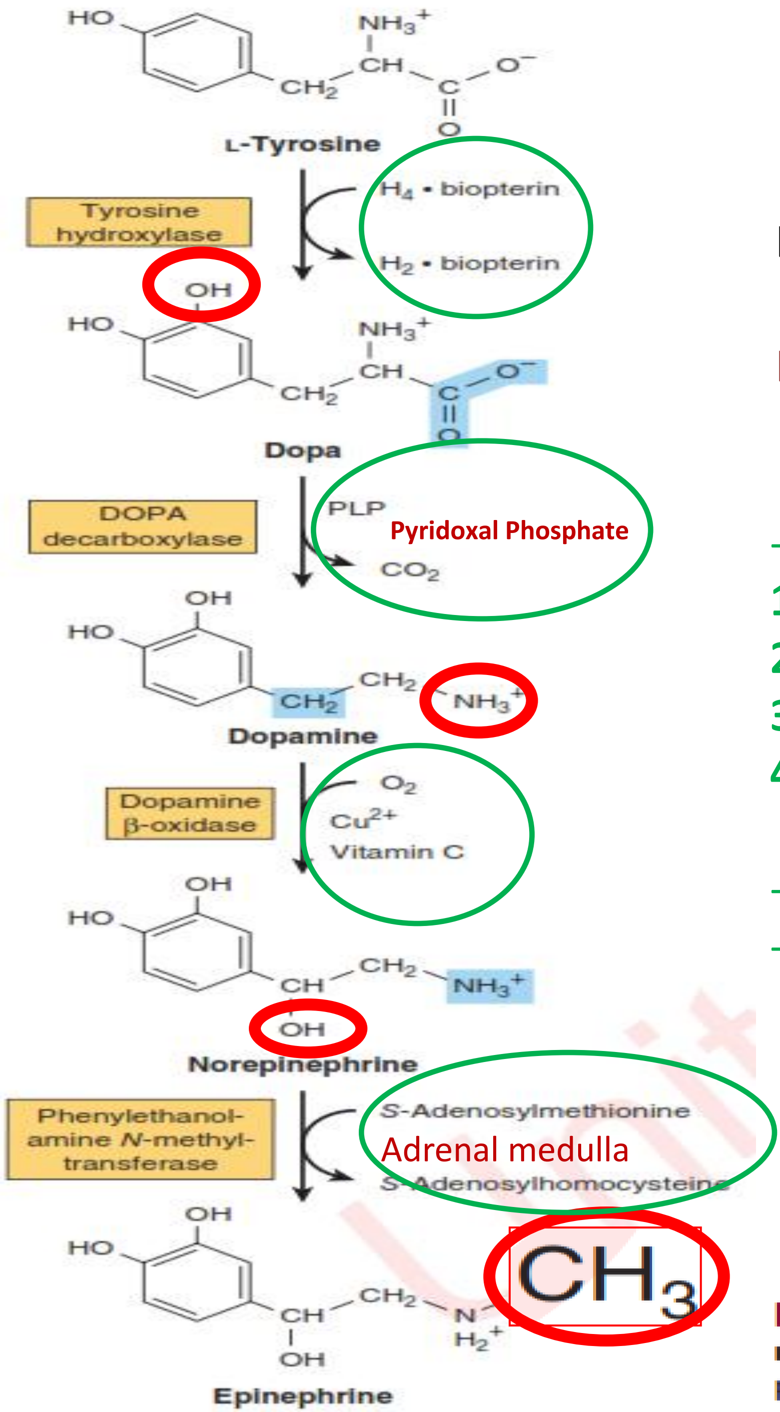
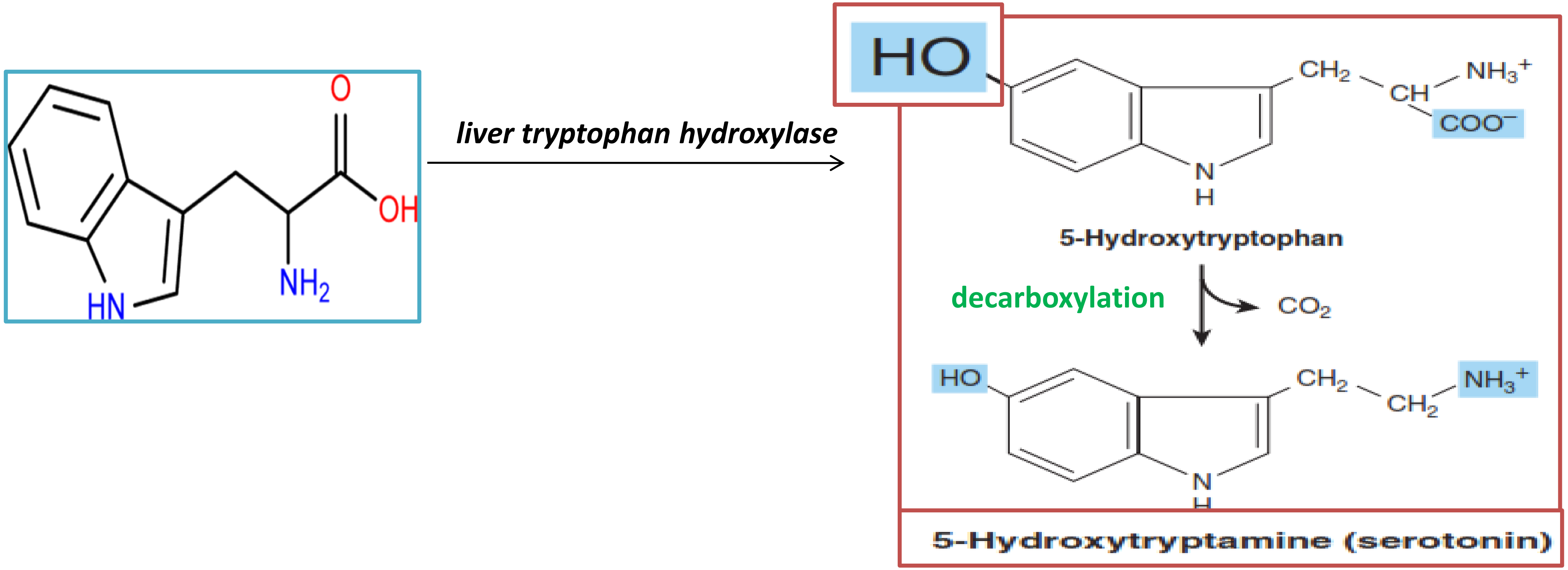


FIGURE 30–12 Conversion of tyrosine to epinephrine and norepinephrine in neuronal and adrenal cells. (PLP, pyridoxal phosphate.)

Serotonin (5-OH-tryptamine)

Potent vasoconstrictor and stimulator of smooth muscle contraction

Tryptophan is the precursor



You have to know just these things:

- **Serotonin catabolism is done by different ways:**

1. **Conversion to melatonin which is responsible for sleeping cycle**
2. **Excretion as conjugated molecules.**

- **Some patients who are suffering from depression can take iproniazid which inhibit the action of mono amino oxidase enzyme(MAO) an enzyme responsible for serotonin catabolism.**

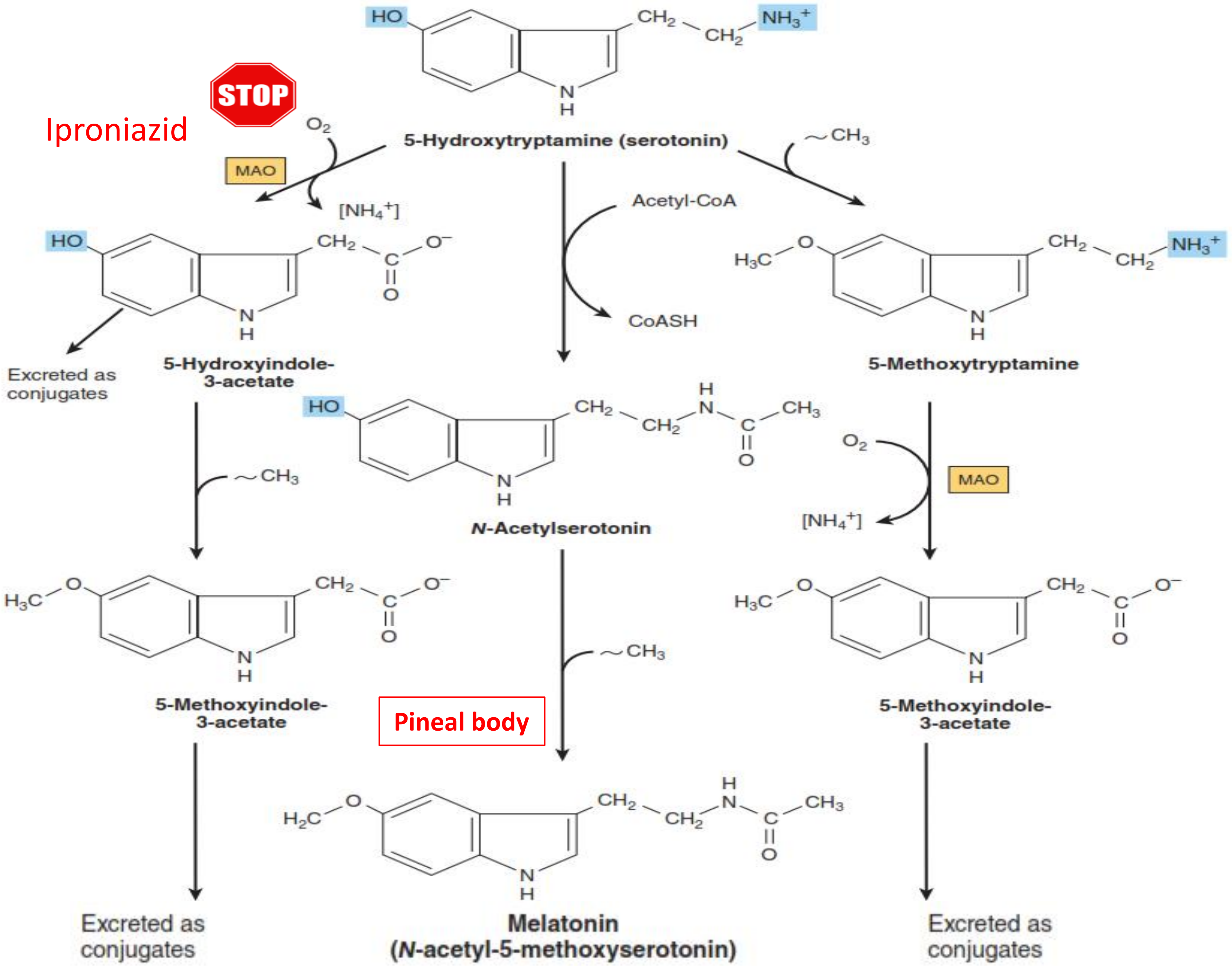
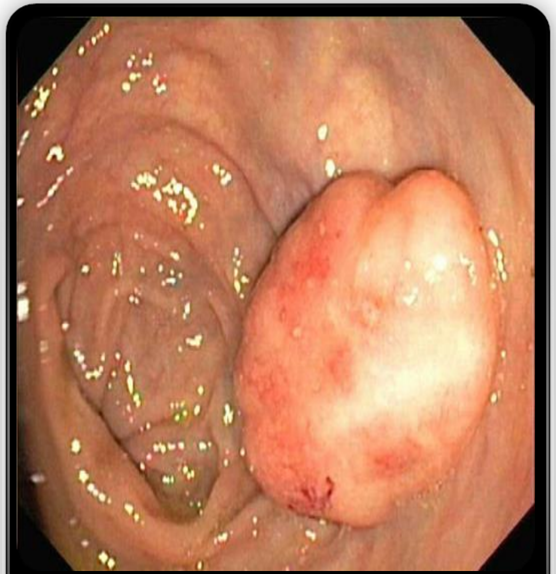


FIGURE 30–11 Biosynthesis and metabolism of serotonin and melatonin. ($[NH_4^+]$, by transamination; MAO, monoamine oxidase; $\sim CH_3$, from S-adenosylmethionine.)

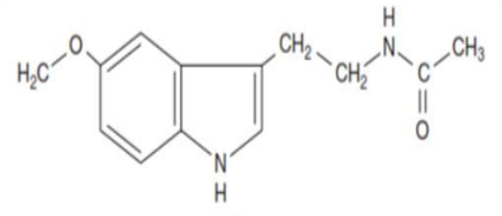
Special secretion of Serotonin

- In carcinoid (Argentaffinoma), tumor cells overproduce serotonin.

Colorectal cancer



- Circulating melatonin is taken up by all tissues, including brain, but is rapidly metabolized by hydroxylation followed by conjugation with sulfate or with glucuronic acid.



Melatonin

Glutamate metabolism

- There are some types of integrations between amino acids metabolism and glucose metabolism like glycolysis and Kreps cycle here is an example of metabolism of glutamate in Kreps cycle.

- from this slide you have to know the amino acids that are used to generate glutamate(Arg, His, Gln and Pro).

- Also you have to know how does glutamate is converted to alpha ketoglutarate by transamination in presence of another ketoacid that will be converted to amino acid(we discussed this thing in slide 8)

- There are two types of amino acids:
- Ketogenic that produces Acetyl-coA
- glucogenic

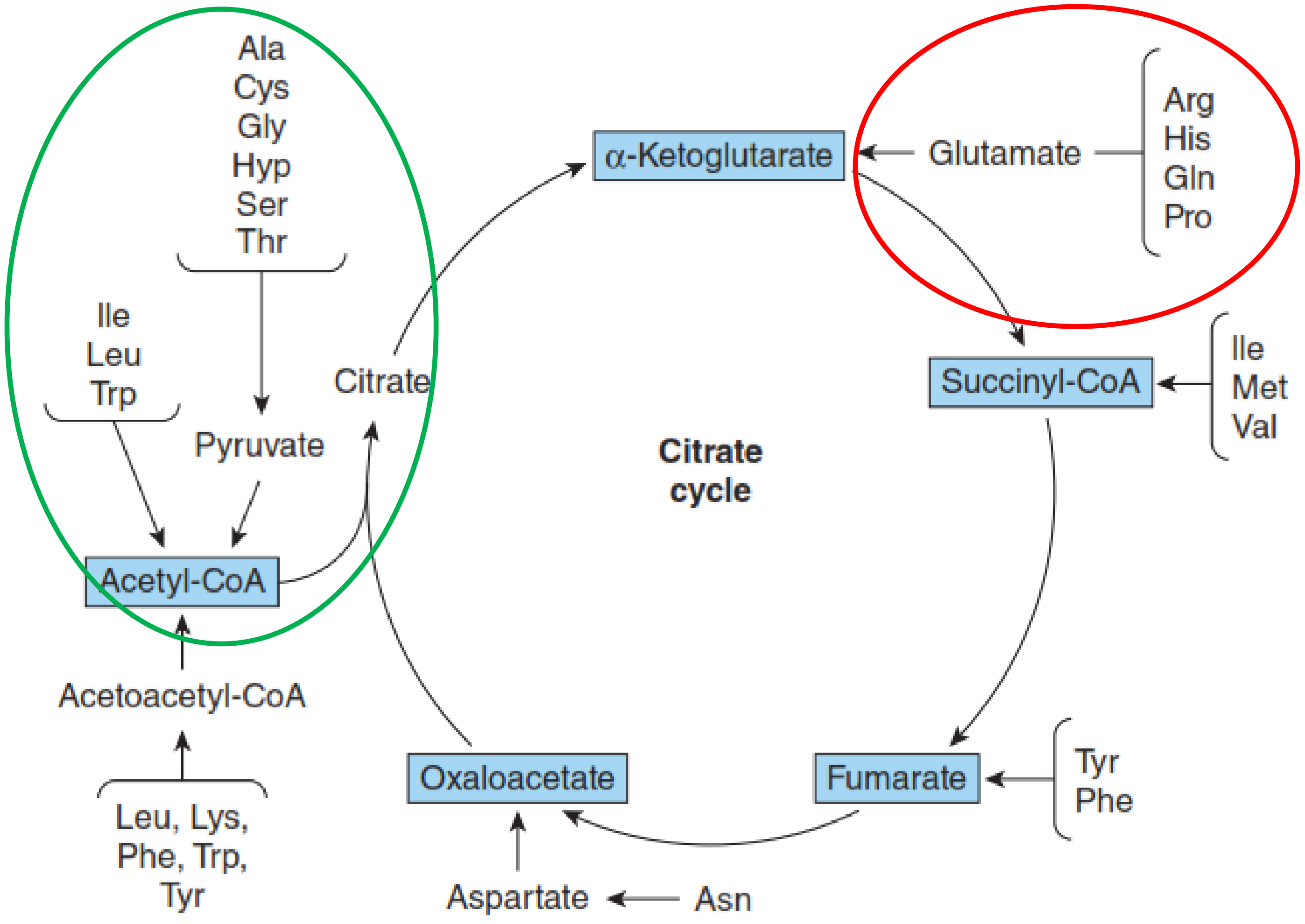


FIGURE 29–1 Overview of the amphibolic intermediates that result from catabolism of the protein amino acids.

Regarding to the previous slide

- **We said before that some amino acids could be used to generate energy but at the same time we don’t rely on them to produce high amount of energy that the reason why we store fats and carbohydrate but we don’t store amino acids rather than this we use them as structural units and in metabolic reactions.**

- **At some cases like fasting or starvation we use them to produce energy but in this case high amount of nitrogen will be produced which will be converted to ammonia(a toxic material).**

- **As a protection mechanism against ammonia the body produces urea.**

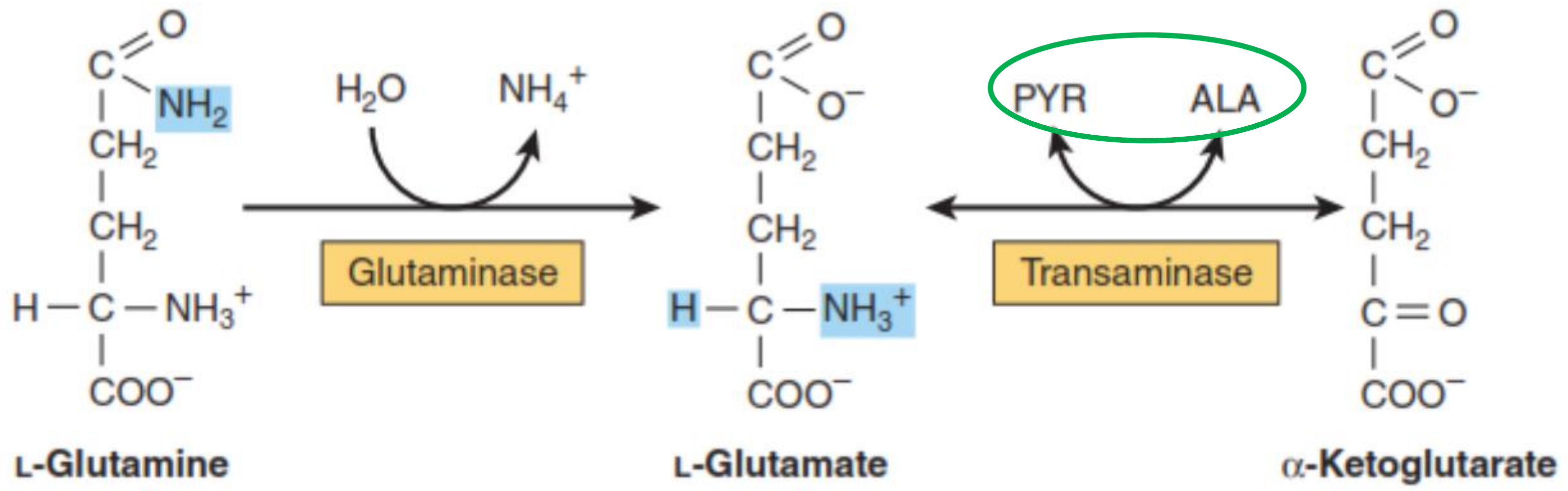
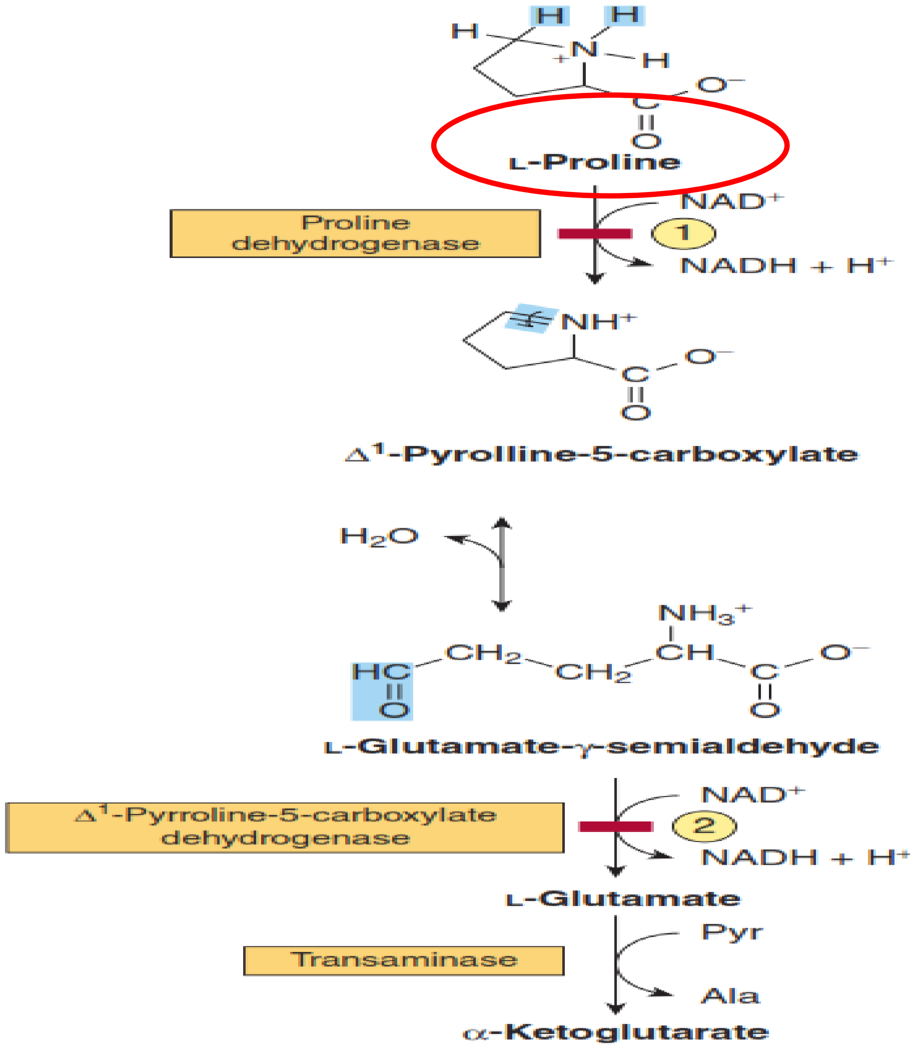
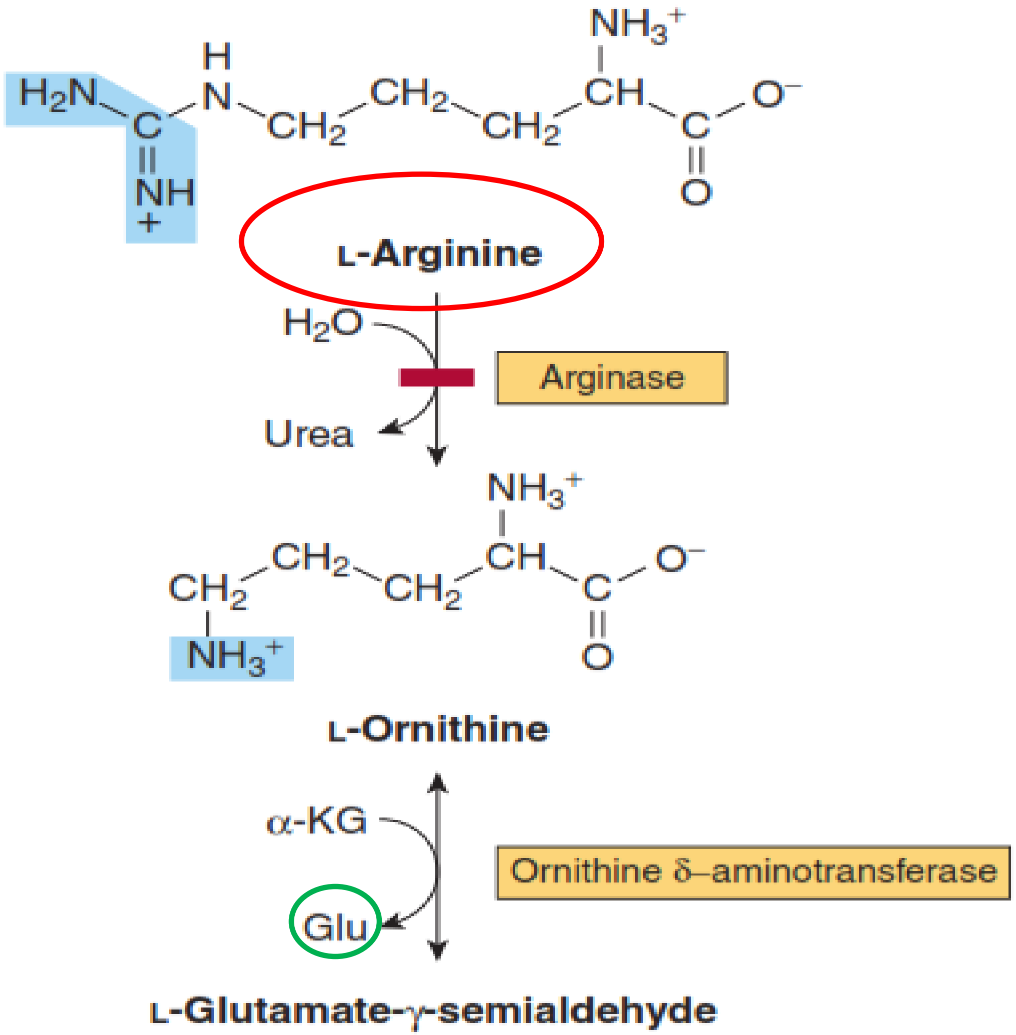


FIGURE 29–2 Catabolism to amphibolic intermediates of L-asparagine (top) and of L-glutamine (bottom). (ALA, L-alanine; PYR, pyruvate.) In this and subsequent figures, blue highlights emphasize the portions of the molecules that are undergoing chemical change.

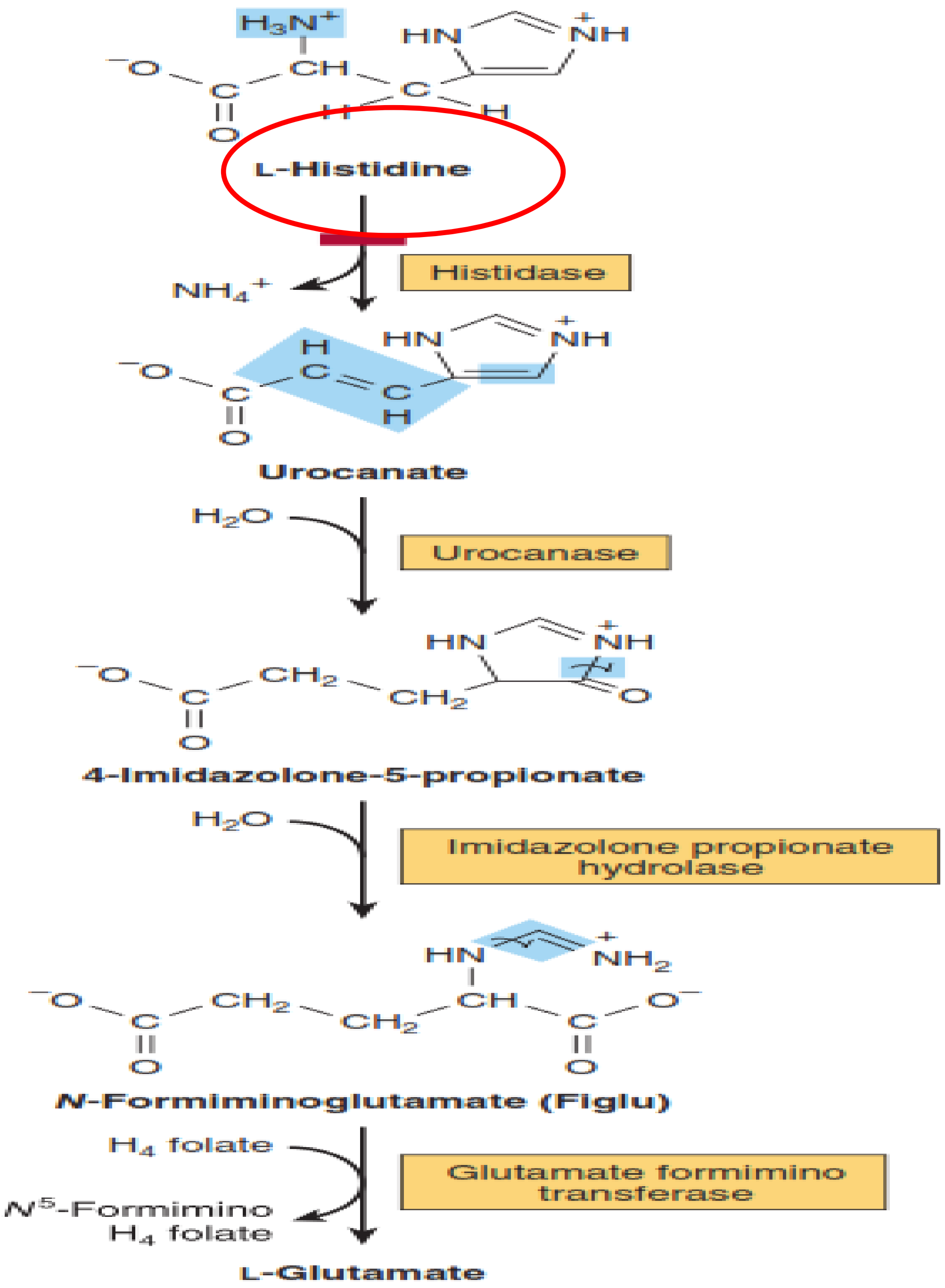
- **you have to know these things:**
- **Glutamine is converted to glutamate by deamination step that is done by glutaminase enzyme.**
- **Glutamate is converted to glutamine by amination reaction.**
- **Glutamate is converted to alpha ketoglutarate by transamination with another ketoacid or vise versa.**
- **As an example is the conversion between pyruvate and alanine.**
- **The glutamate gives pyruvate amine group so it’s converted to alanine and after donating of amine group the glutamate converts to keto-acid**
- **Glutamine works as amine group carrier that generated in the body tissues.**



Here are the steps that indicate how such amino acids are converted to glutamate, in proline you have to know that there are a complex reactions and dehydrogenases enzymes that indicate a tough oxidation process in order to convert proline to glutamate



Arginine is converted to ornithine by arginase enzyme and then to Glu by ornithine delta aminotransferase



Not important, just to know that glutamate is produced by His.

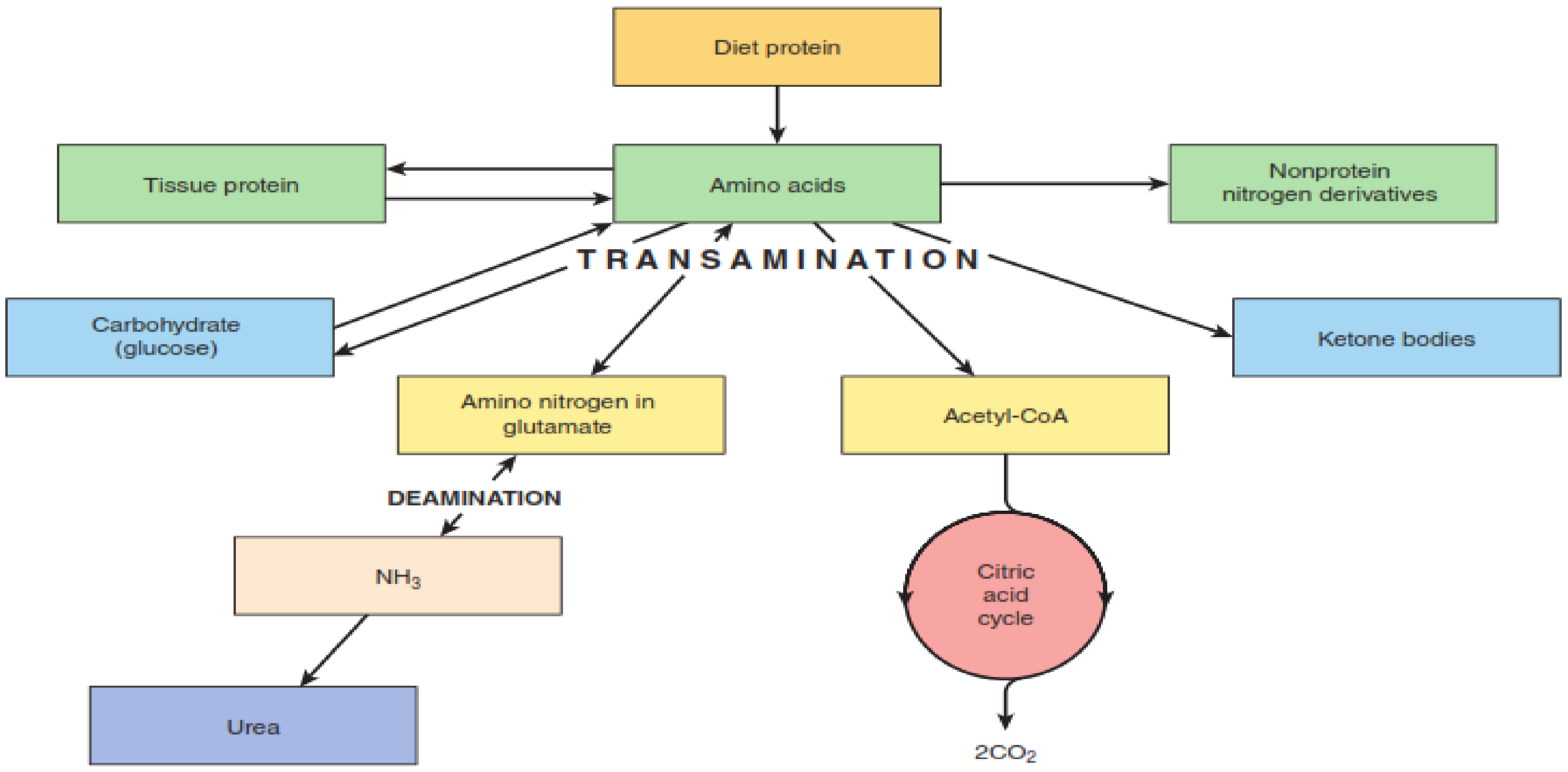


FIGURE 14–4 Overview of amino acid metabolism showing the major pathways and end products.

Ammonia disposal

This picture indicates the fate of amino acids in our bodies:

- starting from diet
- to structural functions
- or being glucogenic amino acids
- or formation of glutamate
- or being ketogenic amino acids
- and nitrogen derivatives

Brain peptides as neurotransmitters

Numerous peptides appear to be neurotransmitter candidates in the brain.

Such as:

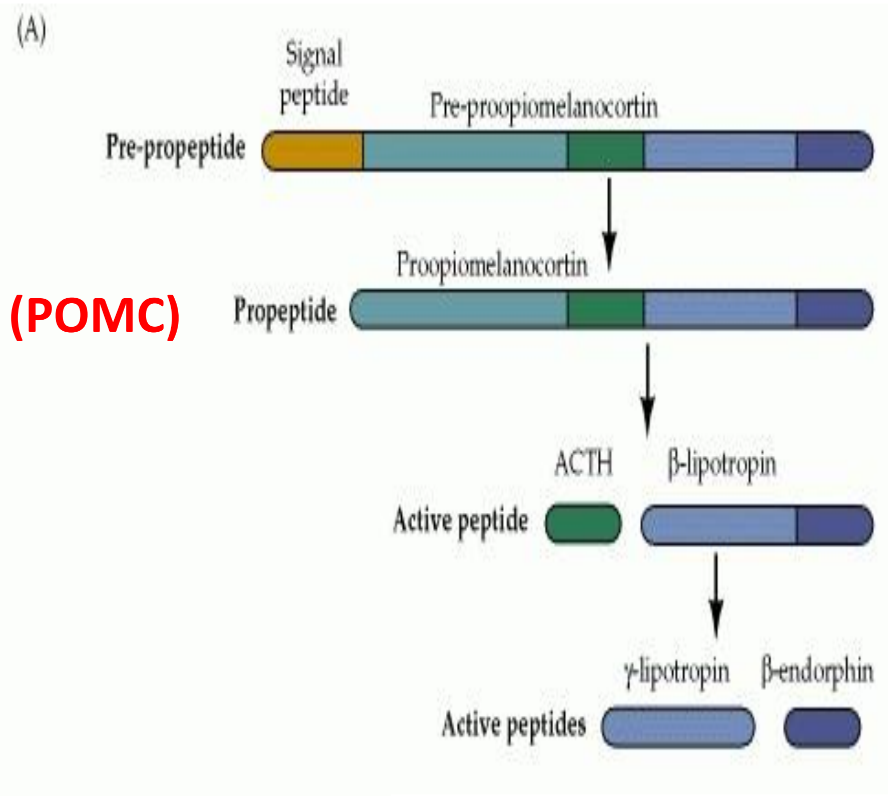
1. ***Opioid peptide*** (more than 20 opioid peptides) grouped into three classes:
   a. Endorphins
   b. Enkephalins: in the head
   c. Dynorphins **:** generally associated with negative emotional states.

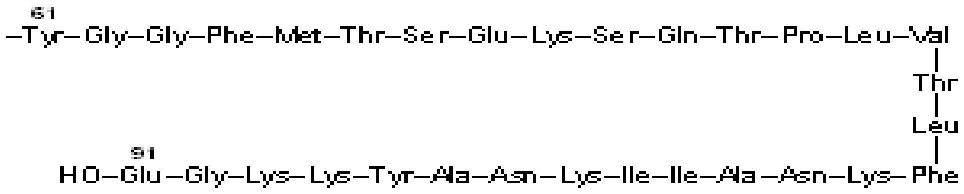
   These precursors are the product of three distinct genes (because we said that they are peptides):

   pre-pro-opiomelanocortin, **pre-pro-enkephalin A**, and **pre-pro-dynorphin.**
   A big peptides that have to be cleaved in order to form active substances

2. ***Substance P*** (11-amino acid peptide)
3. ***Posterior pituitary peptides*** **(vasopressin, oxytocin)**

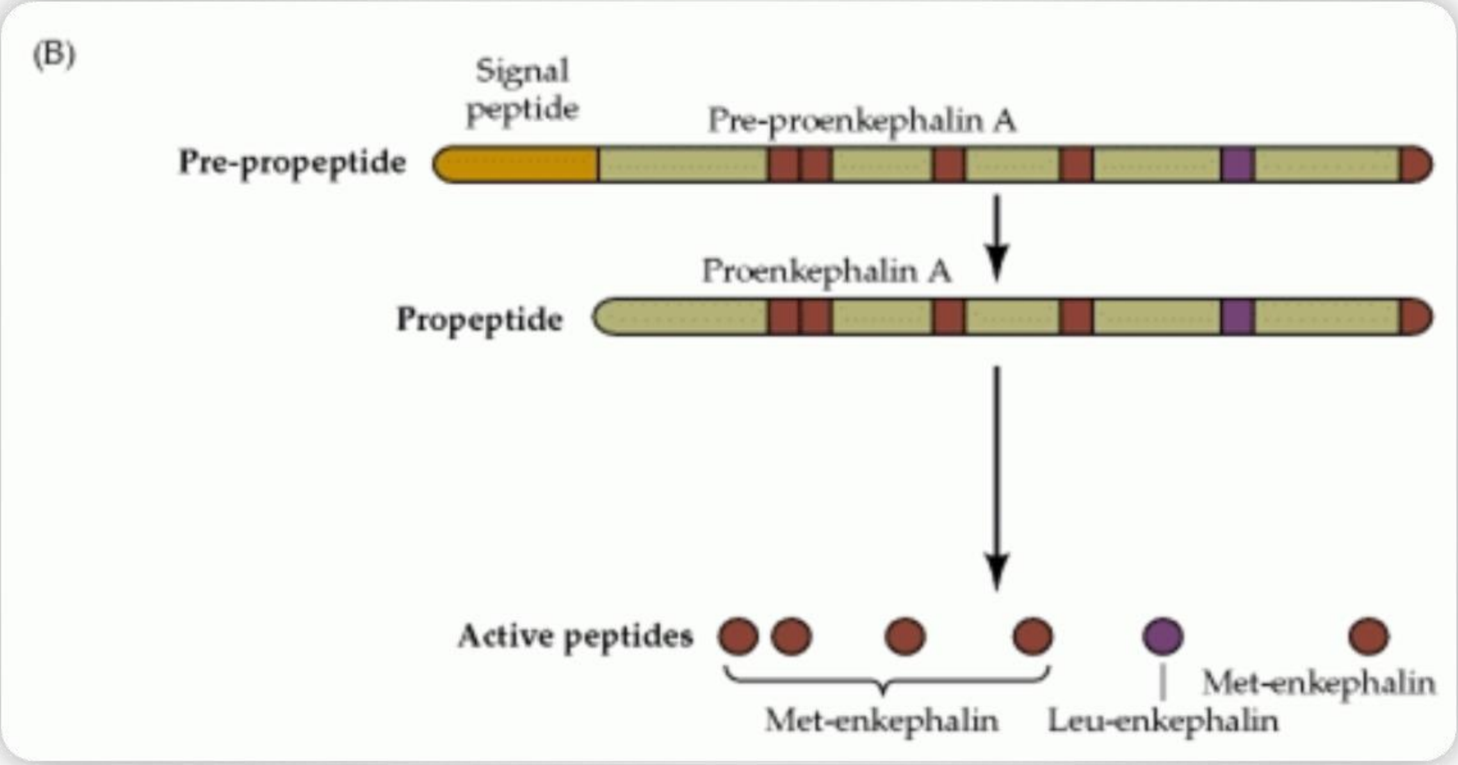
Endorphins





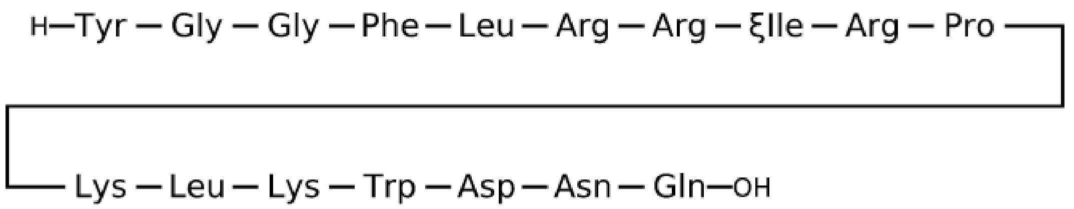
Human β-Endorphin

β-endorphin molecules are produced by the body as portions of larger proopiomelanocortin (POMC) molecules, which are **coded** for by a single gene, synthesized as large molecules, and then cut by enzymes into active subunits.



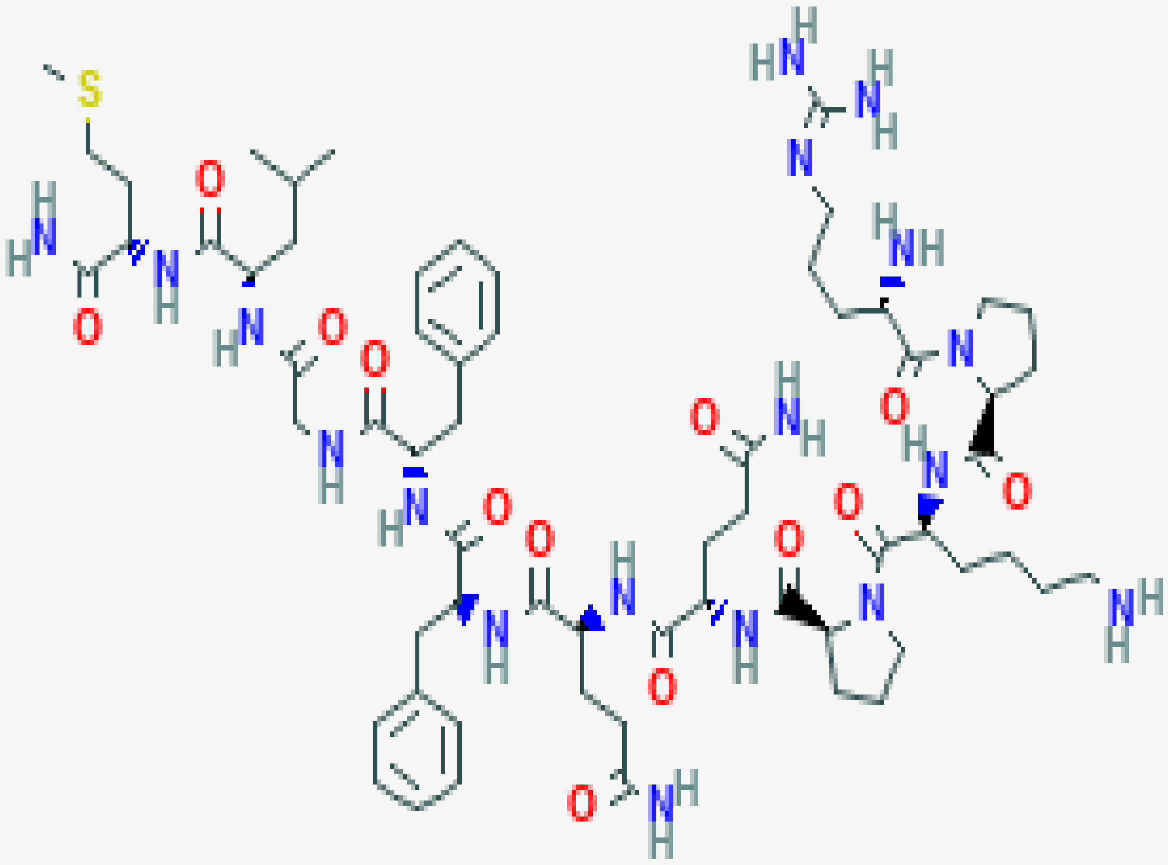
- Signal peptide is important to direct the protein in order to be sorted in certain way.
- Cutting of the signal peptide will generate POMC

Enkephalins



Dynorphins

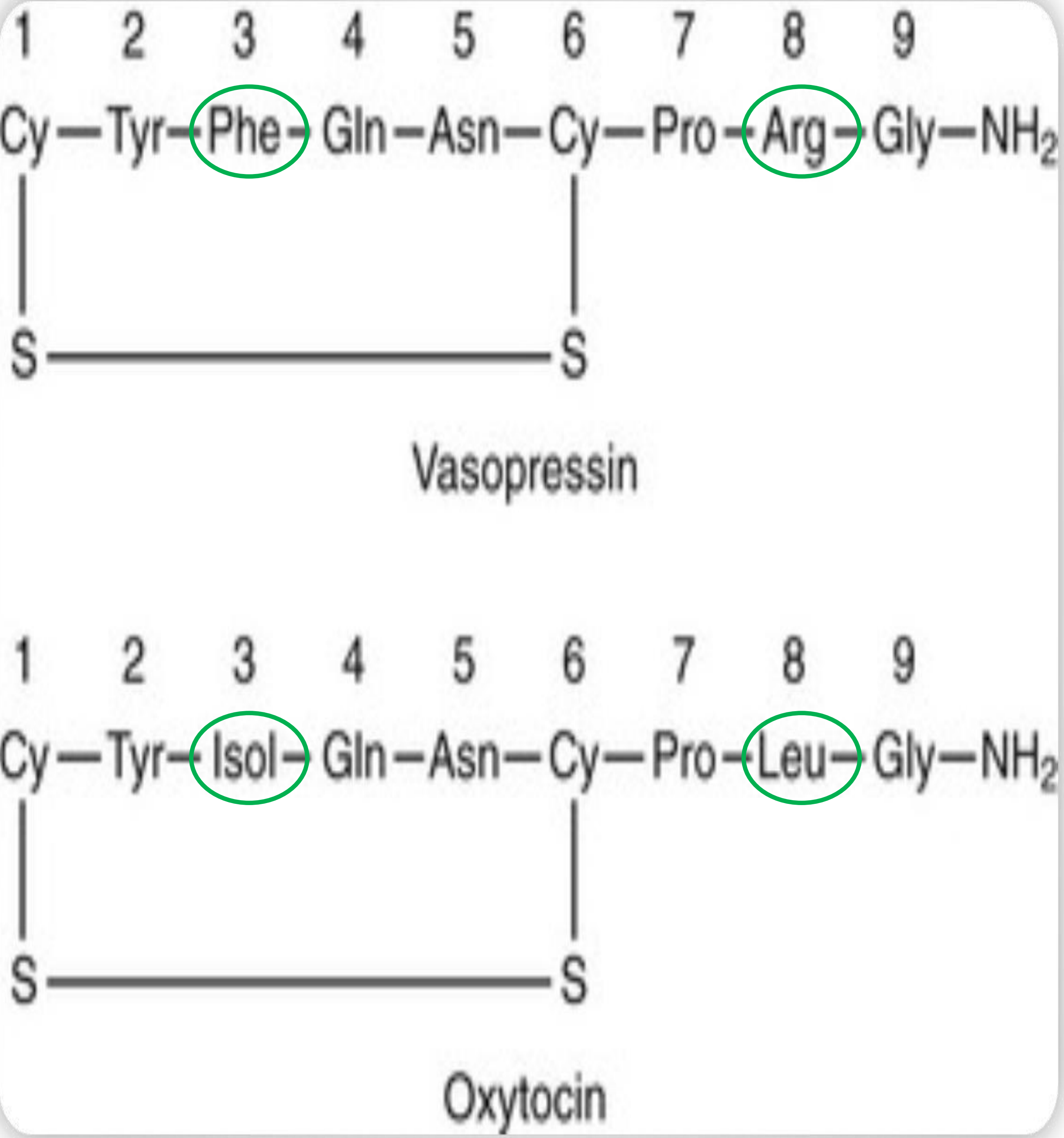
- **Dynorphins because when have more than one type.**
- **Consist of a short type peptide molecule**



Substance P

- Arg-Pro-Lys-Pro-Gln-Gln-Phe- Phe-Gly-Leu-Met-NH2 (RPKPQQFFGLM-NH2) (consist of 11 amino acids peptide, means a short peptide)

- Associated with inflammatory and pain•



Vasopressin and Oxytocin

- A very similar peptides that are generated by the pituitary gland.
- Have differences at position number 3 and number 8.
- Both have s-s bond at the same position which is (1 and 6).