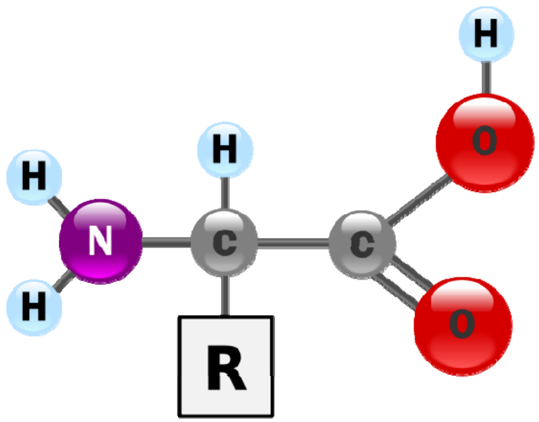
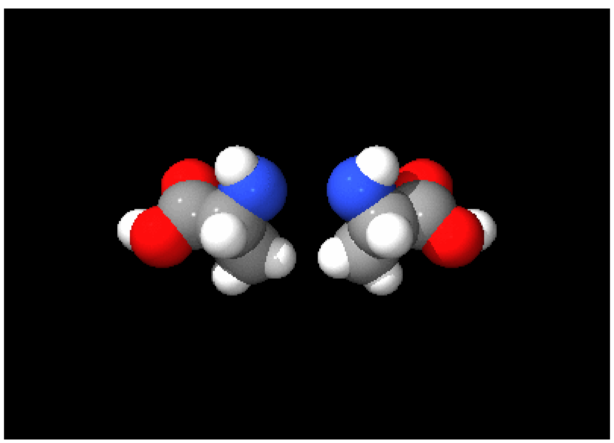
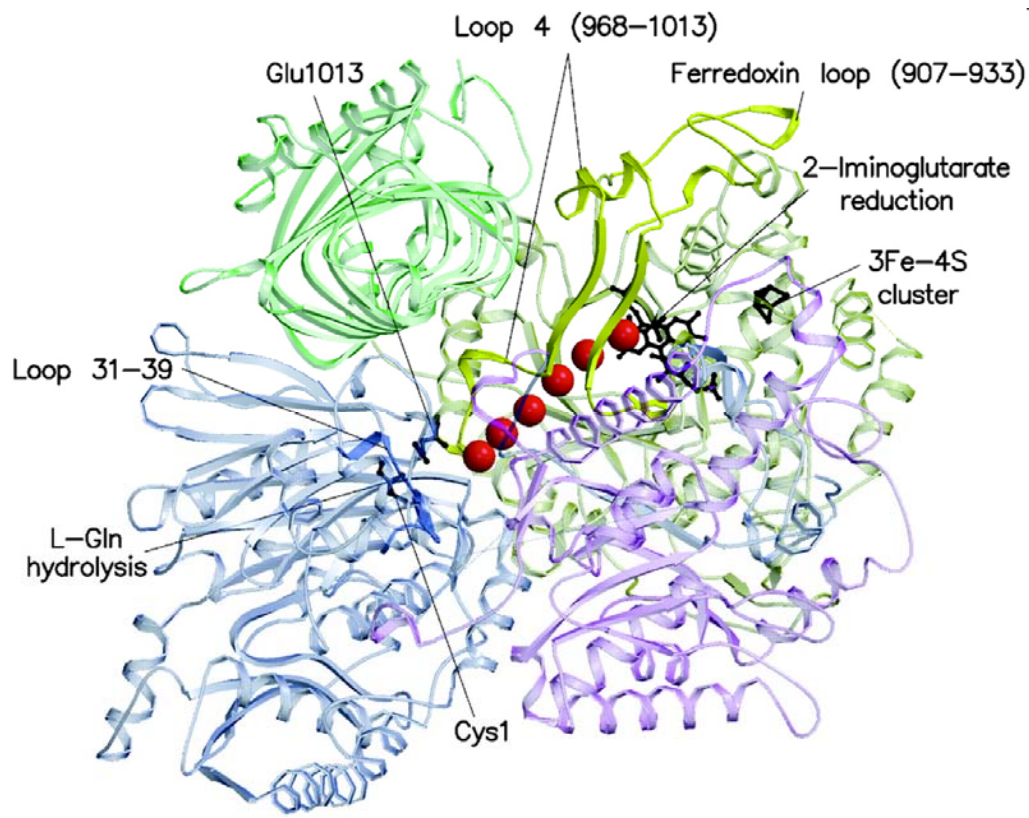
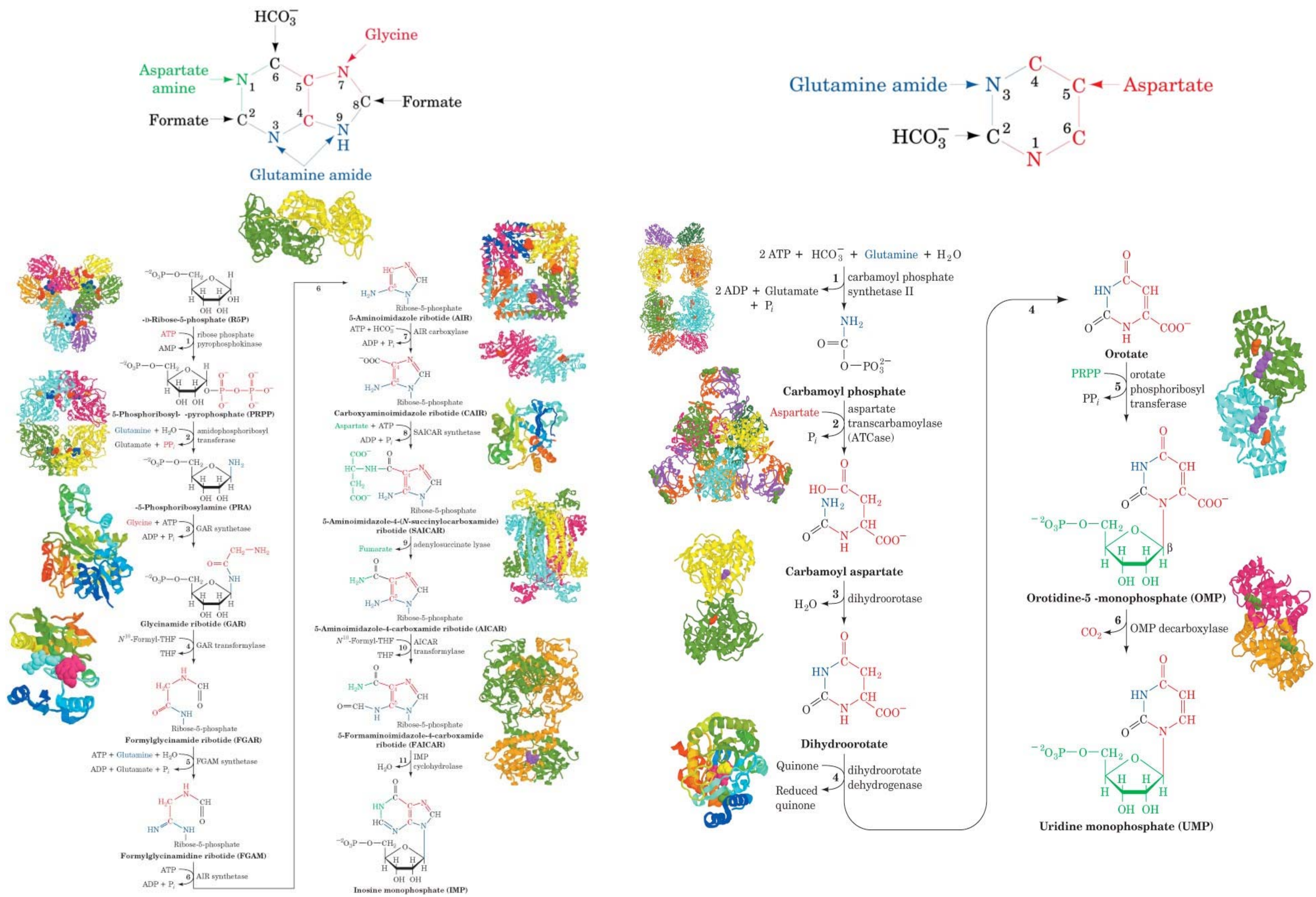
Amino Acid Metabolism







Last Week...



HCO3−
Glycine
Aspartate amine
Formate
Formate
Glutamine amide
Glutamine amide
Aspartate
HCO3−
D-Ribose-5-phosphate (R5P)
ribose phosphate pyrophosphokinase
5-Phosphoribosyl-α-pyrophosphate (PRPP)
amidophosphoribosyl transferase
β-5-Phosphoribosylamine (PRA)
GAR synthetase
Glycinamide ribotide (GAR)
GAR transformylase
Formylglycinamide ribotide (FGAR)
FGAM synthetase
Formylglycinamidine ribotide (FGAM)
AIR synthetase
5-Aminoimidazole ribotide (AIR)
AIR carboxylase
Carboxyaminoimidazole ribotide (CAIR)
SAICAR synthetase
5-Aminoimidazole-4-(N-succinylocarboxamide) ribotide (SAICAR)
adenylosuccinate lyase
5-Aminoimidazole-4-carboxamide ribotide (AICAR)
AICAR transformylase
5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)
IMP cyclohydrolase
Inosine monophosphate (IMP)
2 ATP + HCO3− + Glutamine + H2O
2 ADP + Glutamate + Pi
carbamoyl phosphate synthetase II
Carbamoyl phosphate
Aspartate
Pi
aspartate transcarbamoylase (ATCase)
Carbamoyl aspartate
H2O
dihydroorotase
Dihydroorotate
Quinone
Reduced quinone
dihydroorotate dehydrogenase
Orotate
PRPP
PPi
orotate phosphoribosyl transferase
Orotidine-5′-monophosphate (OMP)
CO2
OMP decarboxylase
Uridine monophosphate (UMP)

Most of the Animal Kingdom = Lazy

- Most higher organisms in the animal kindom don't bother to make all of the amino acids.

  - Instead, we eat things that make the 'essential' amino acids for us

Unsuprisingly, humans are among the laziest animals

Not really essential

Essential	Nonessential
Arginine[a]	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Proline
Tryptophan	Serine
Valine	Tyrosine

[a]Although mammals synthesize arginine, they cleave most of it to form urea (Sections 26-2D and 26-2E).

More or less essential

Nucleotide Metabolism

- Synthesis of:

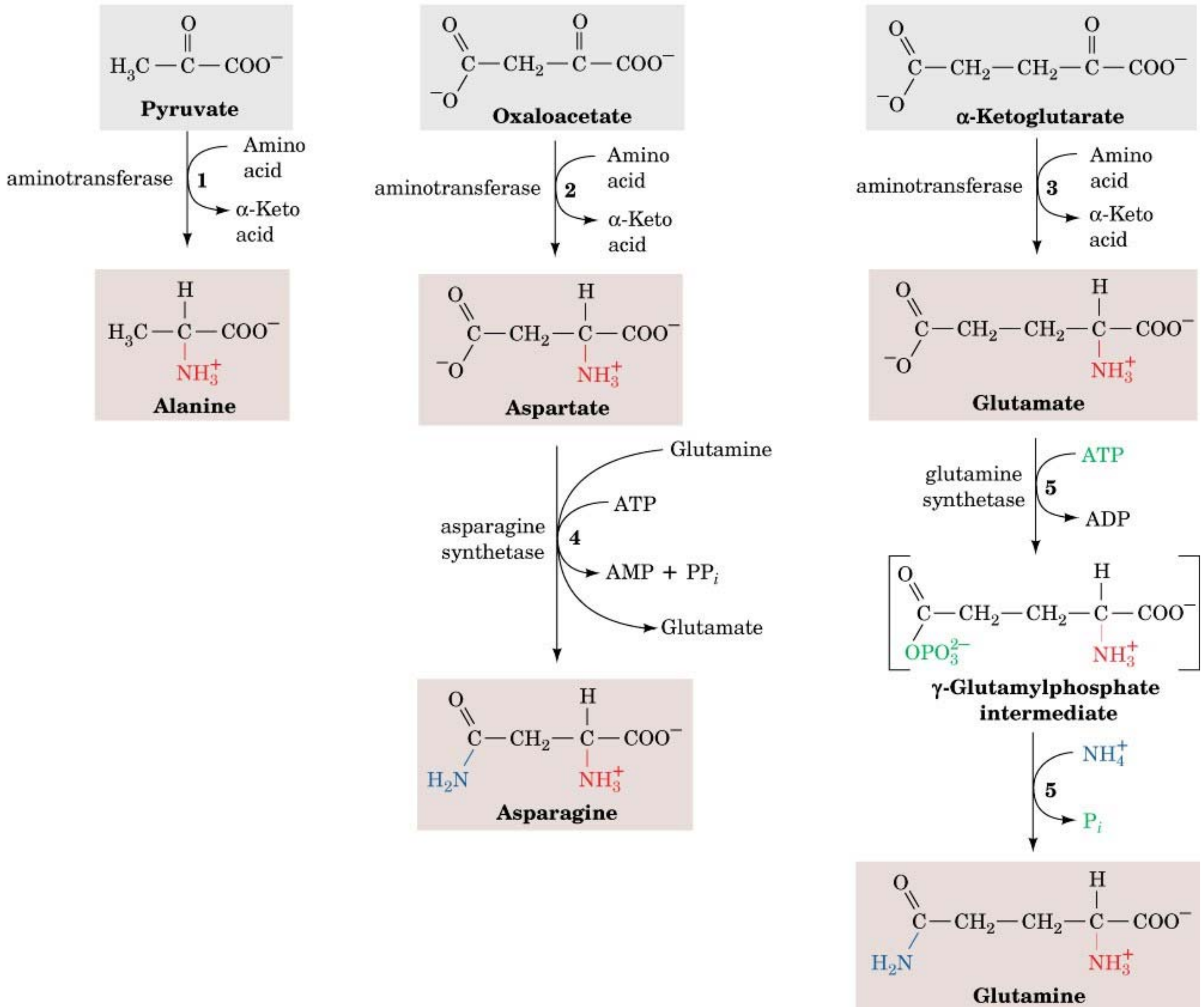
Alanine

Aspartate

Asparagine

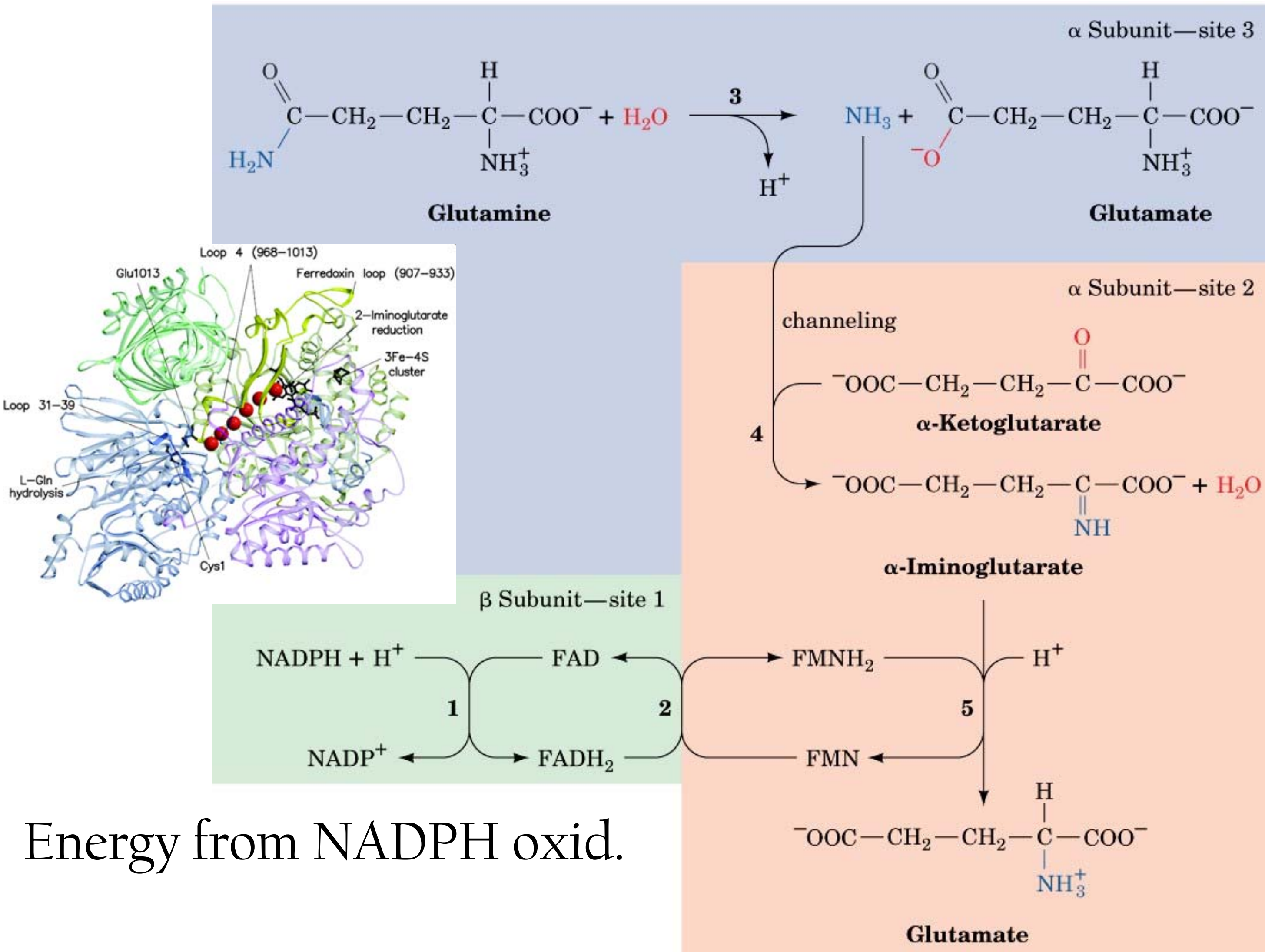
Glutamate

Glutamine



Glutamate Synthase

- Plants and lower organisms use a synthase to make glutamate



Glu #1

Energy from NADPH oxid.

Glu #2

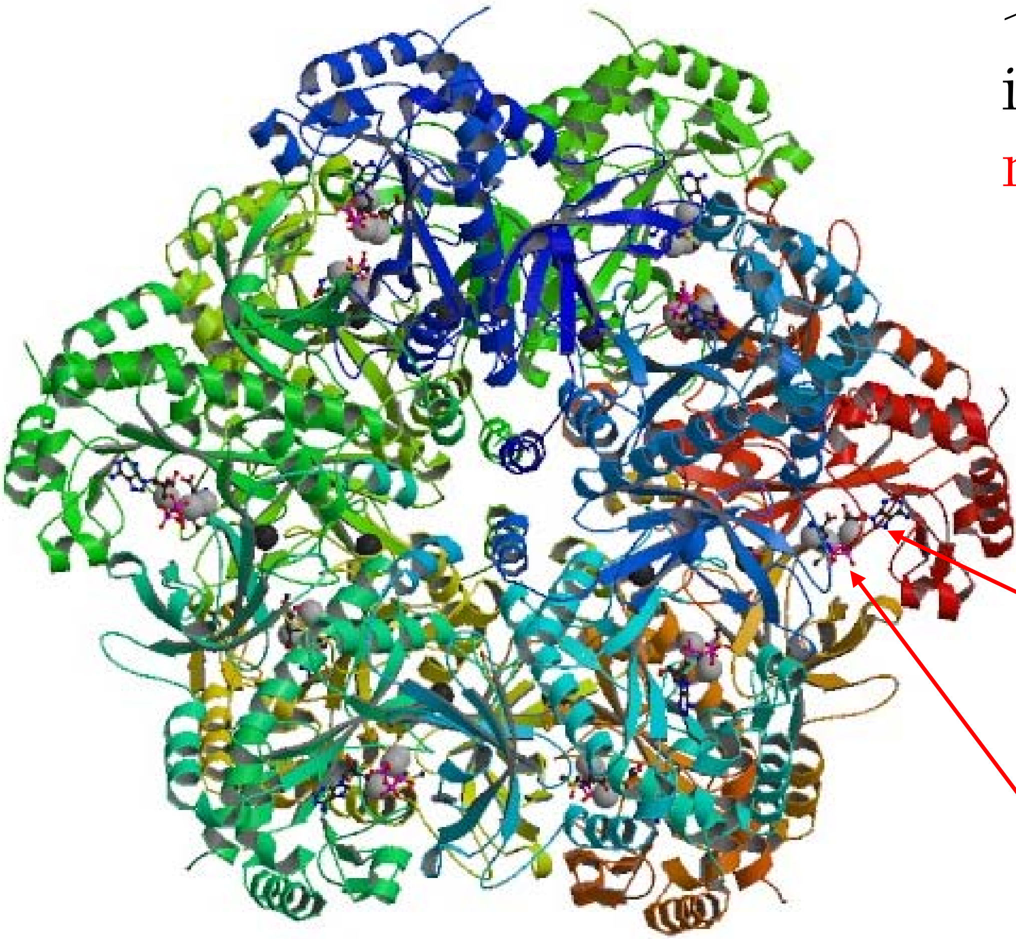
Overall: NADPH + H^+ + glutamine + α-ketoglutarate ⟶ 2 glutamate + $NADP^+$

Glutamine Synthetase

- When we make glutamine, we've got to use some precious ATP

- Glutamine synthetase is an important metabolic center for nitrogen metabolism.

- Glutamine is commonly an NH_2 donor (see nucleotide synthesis)



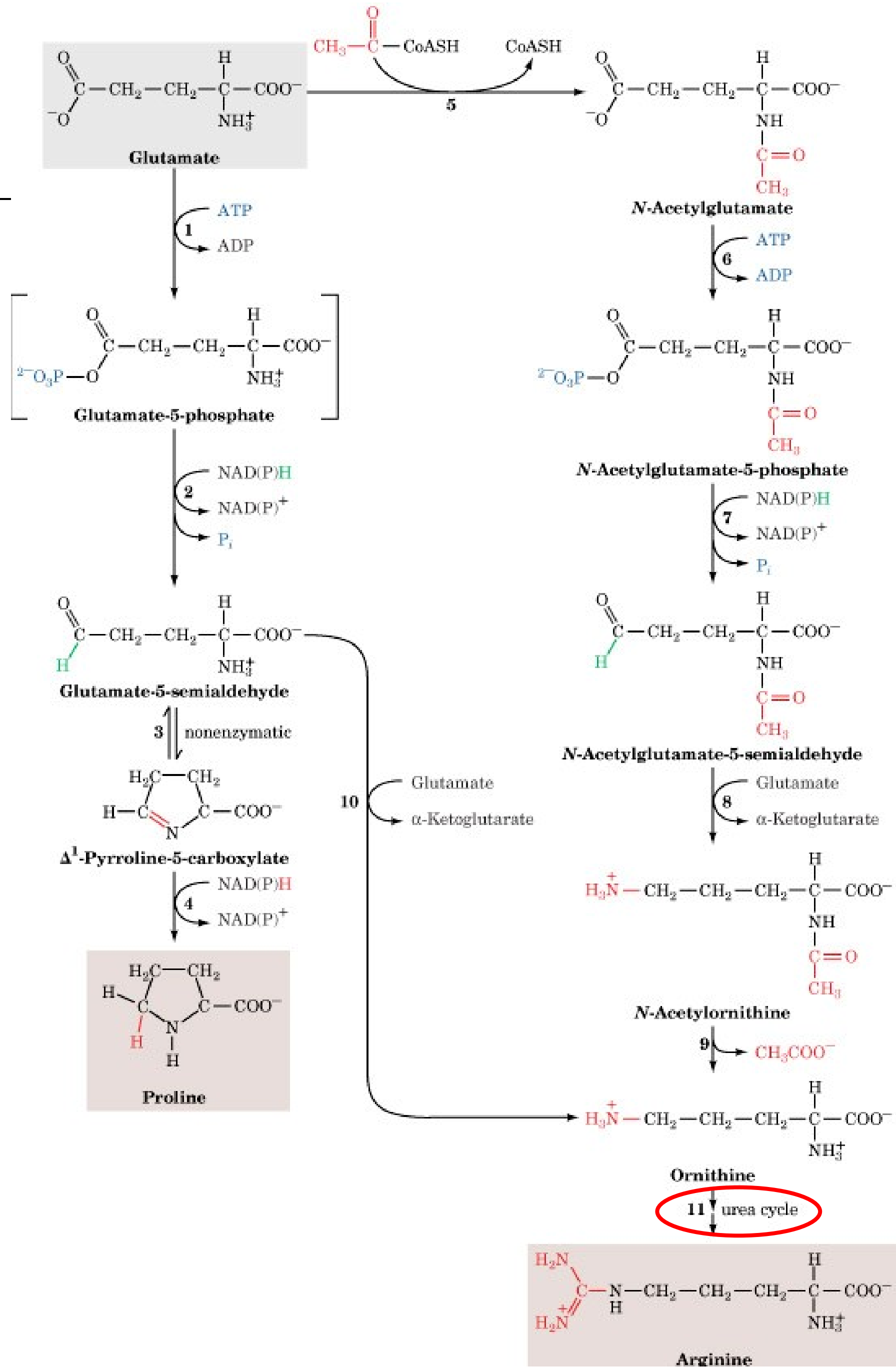
Nucleotide Metabolism

- Synthesis of:

Arginine

Ornithine

Proline



Good for getting rid of excess NH_4^+...

...or making Arg

Amino Acids from 3-Phosphoglycerate

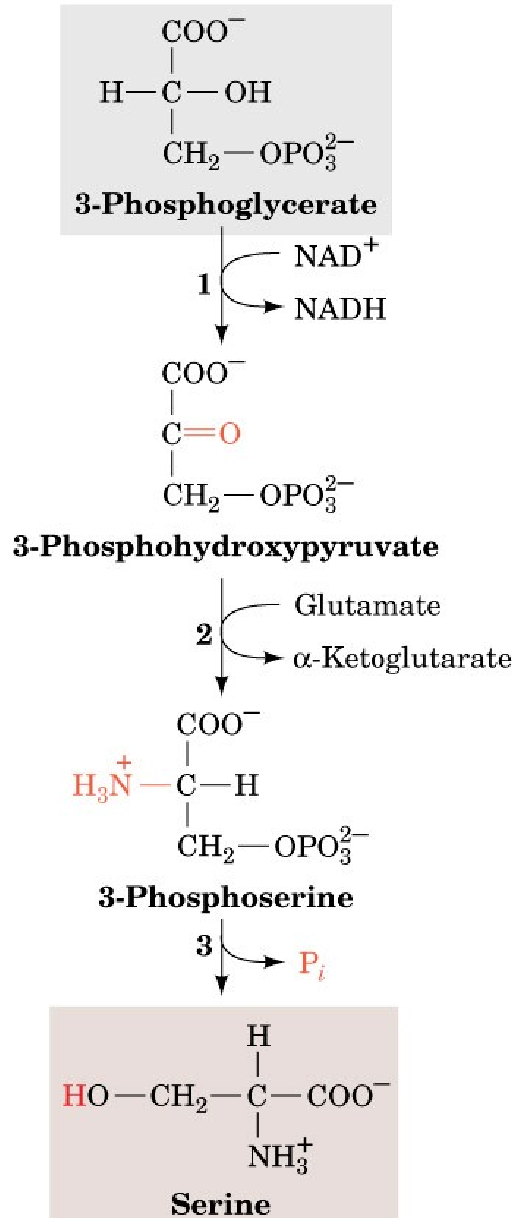
- Synthesis of:

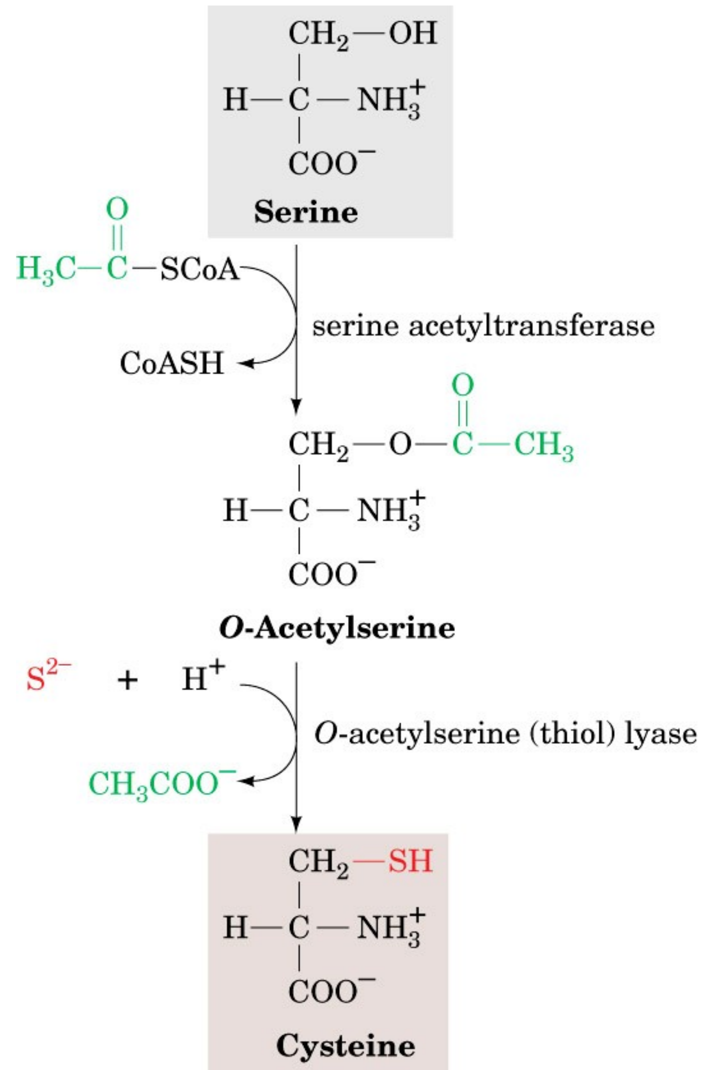
Serine

Cysteine

Glycine

- Made from Serine, can regenerate methylene-tetrahydrofolate





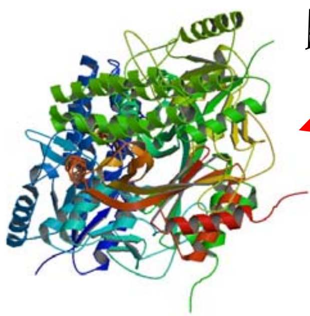
Essential Amino Acids from Aspartate

- Pants synthesize for us:

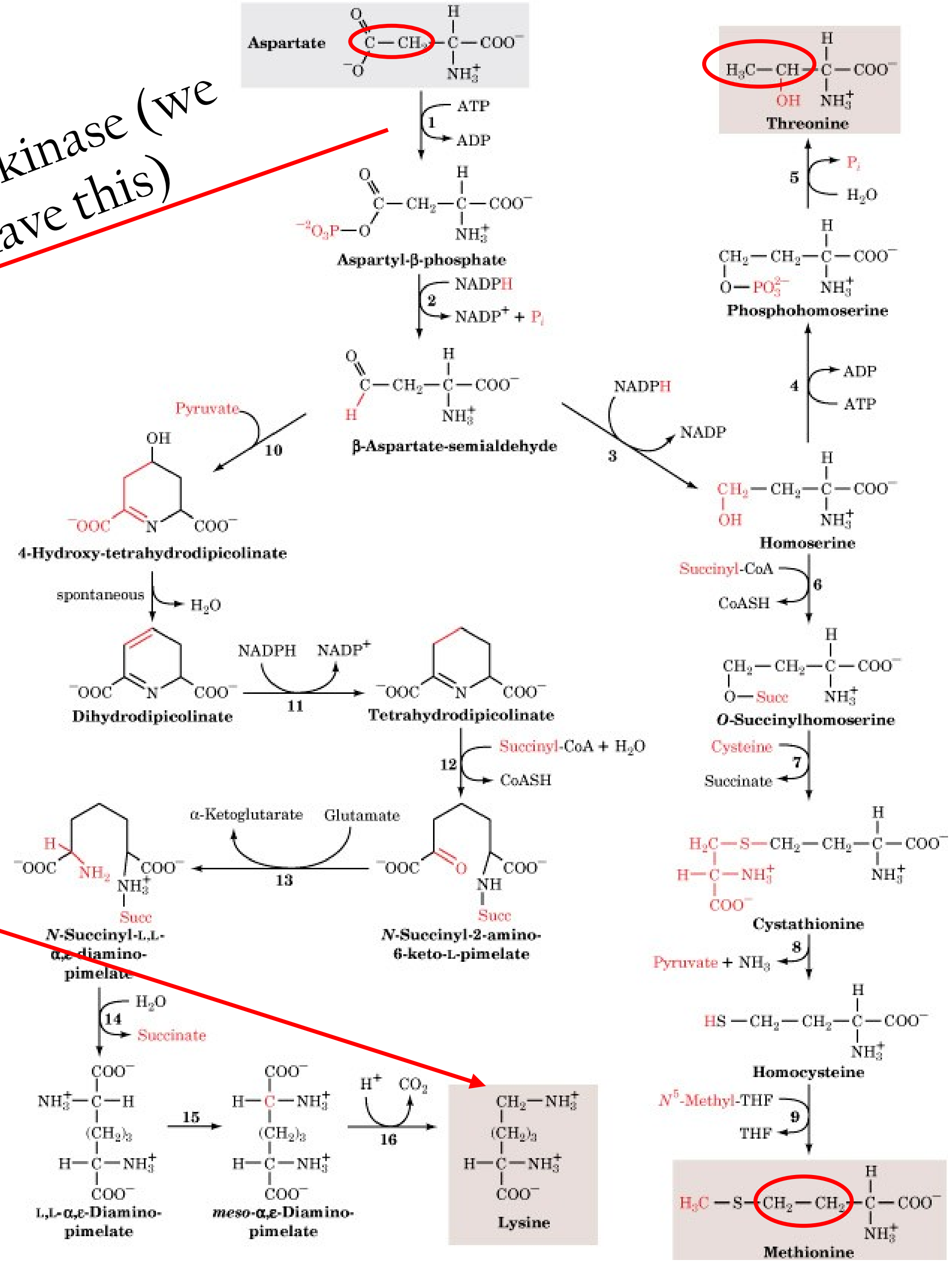
Lysine

Methionine

Threonine



Aspartokinase (we don't have this)



-Hardest (long carbon chain)

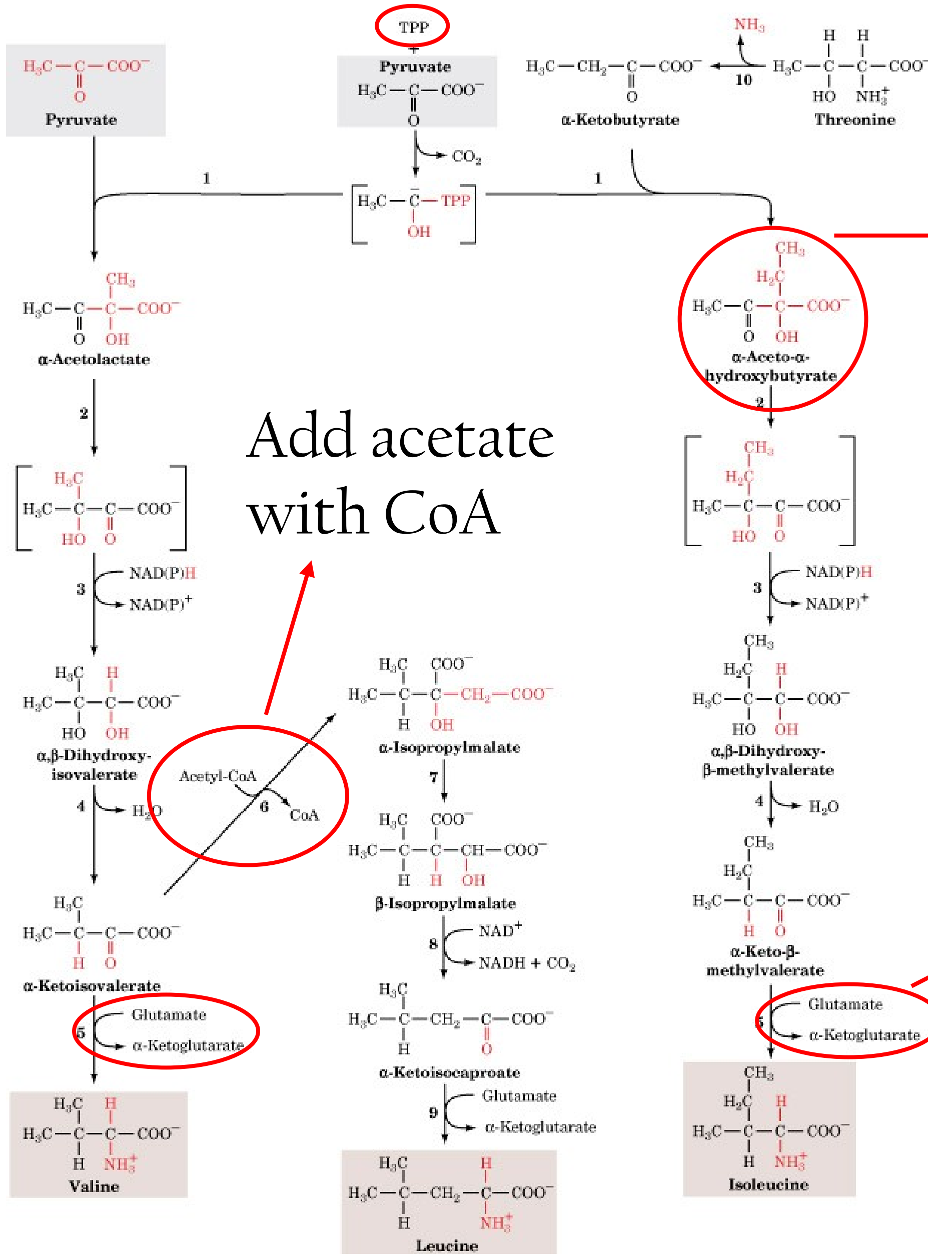
Essential Amino Acids from Pyruvate

- Synthesis of:

Leucine

Isoleucine

Valine



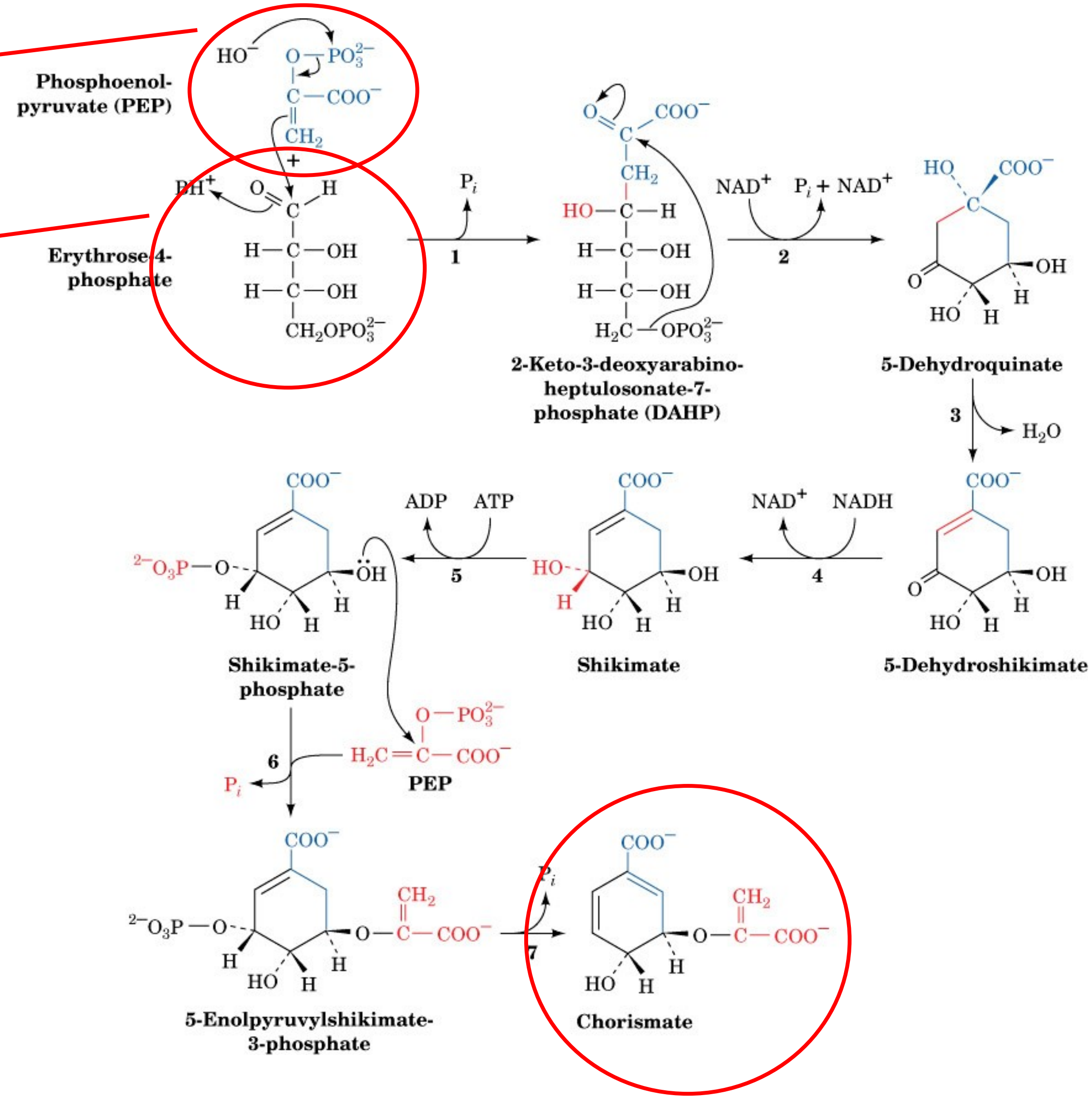
Add acetate with CoA

-Clearly on our way to 'iso'-something

-E.g. Glutamate as NH_2 donor

Chorismate: The Aromatic A.A. Precursor

- There is a single precursor for all 'standard' aromatic amino acids
  - Made from PEP!
  - From the Pentose Phosphate Pathway (an alternative to glycolysis)



Making Aromatic Amino Acids

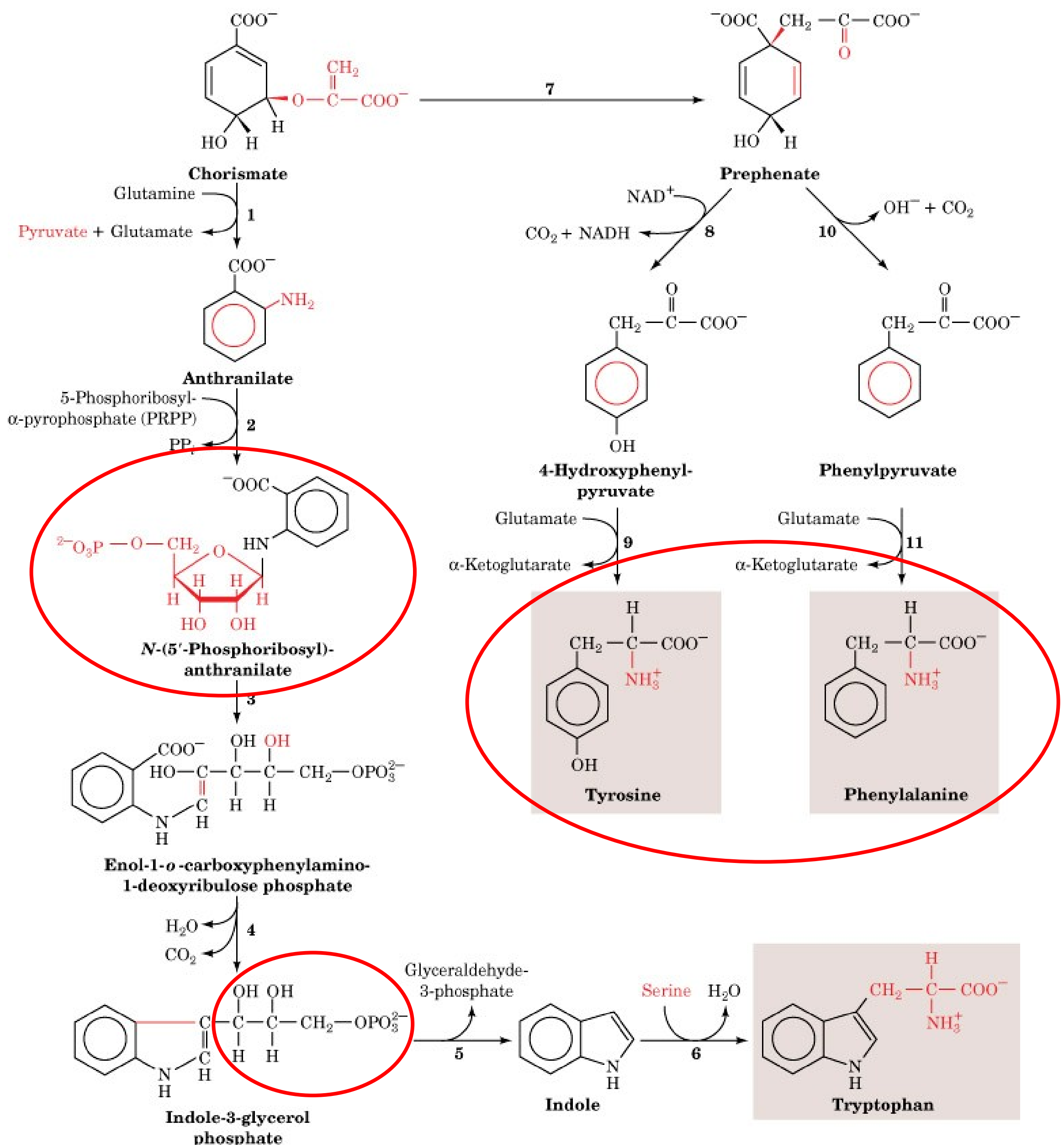
- Synthesis of:

Tyrosine

Phenylalanine

Tryptophan

- We can do a direct hydroxylation of Phenylalanine to give tyrosine



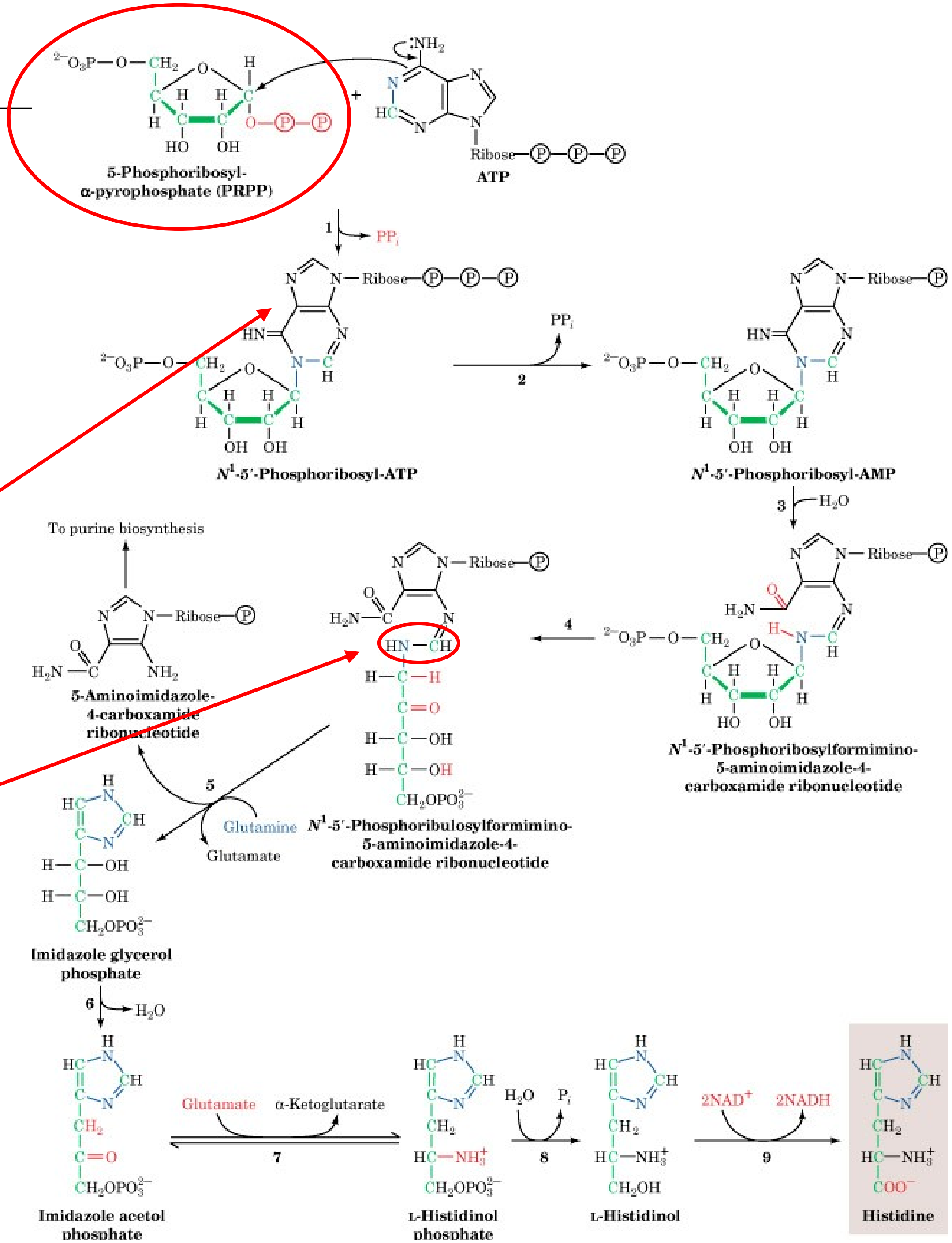
Synthesis of Histidine

- The one amino acid we 'missed' is the essential amino acid Histidine

- Synthesized from PRPP and a purine! (Adenosine)

- The only two groups from ATP

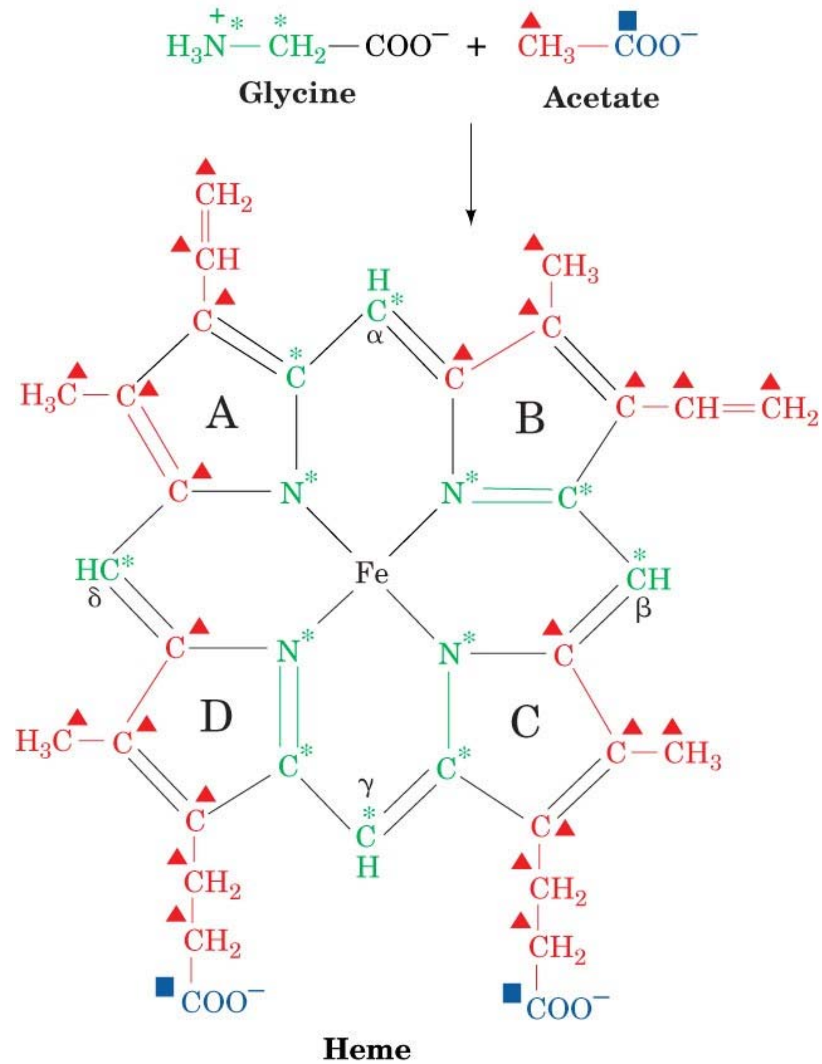
- Could be a 'leftover' from when RNA ruled the world.



Heme Biosynthesis

- In addition to proteins, some amino acids are used to make co-factors and signaling molecules:

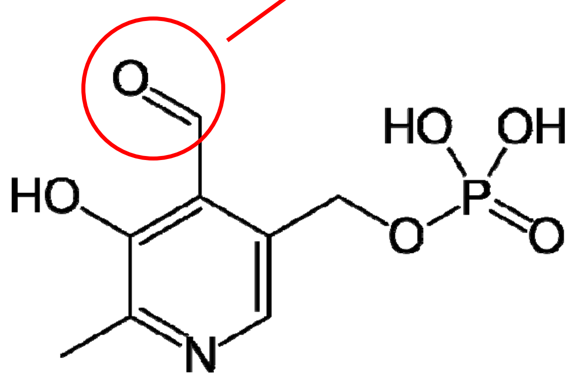
- Porphyrins, for example, are made from Succinyl CoA and Glycine



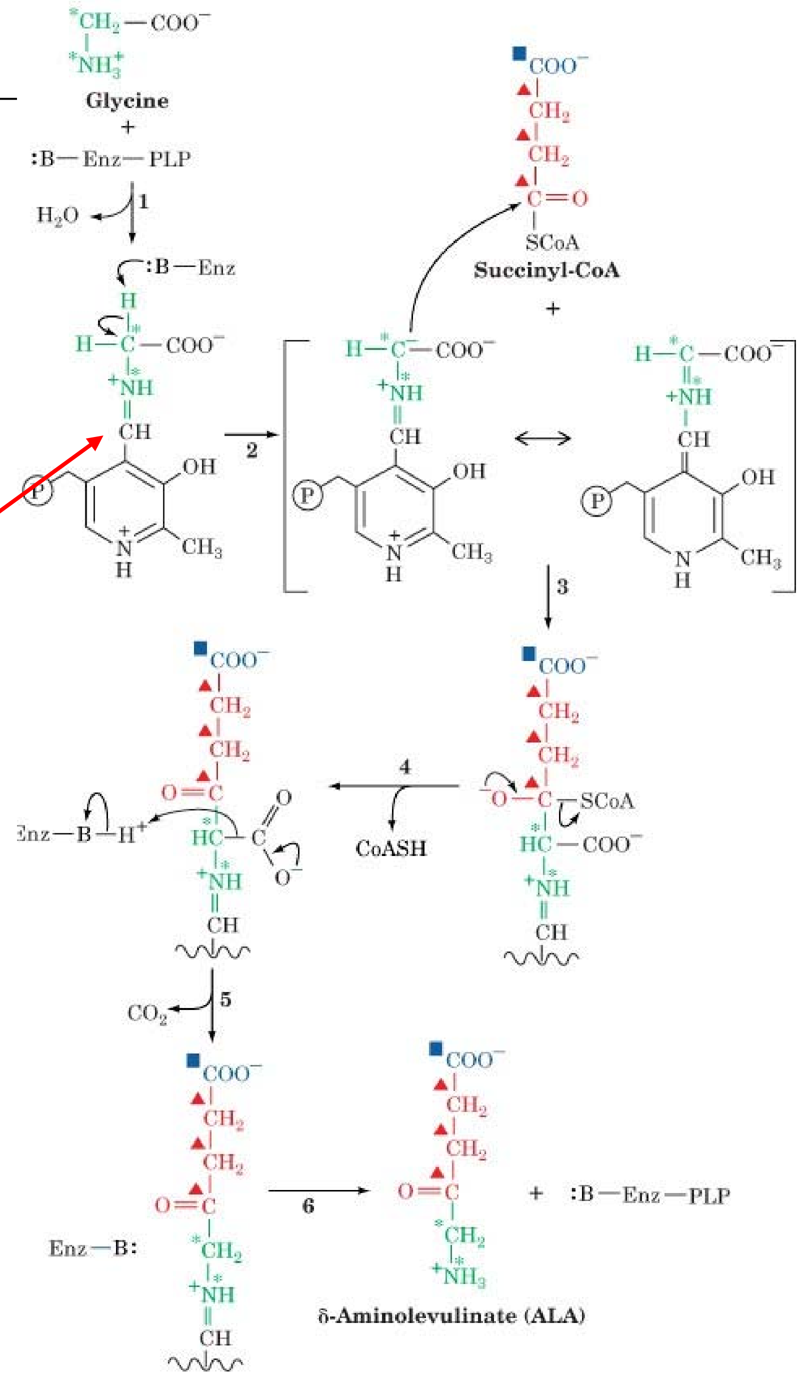
Porphyrin Biosynthesis

- The fundamental unit of porphyrins is δ-aminolevulinate (ALA)

- Made by the pyroxidal phosphate (PLP) dependent enzyme δ-aminolevulinate synthase



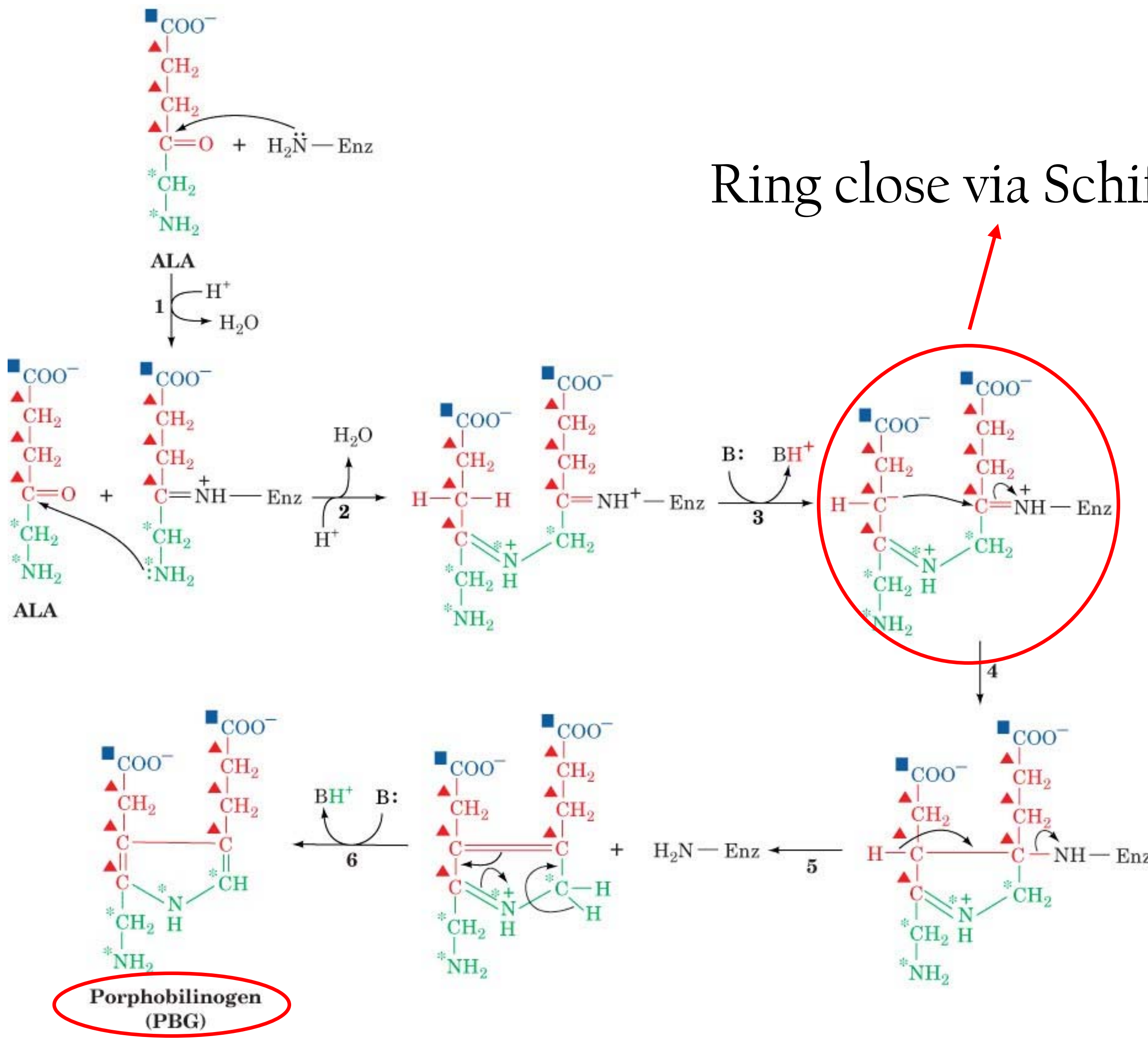
PLP (vitamin B_6)



Porphyrin Biosynthesis

- We then combine 2 ALA into Porphobilinogen

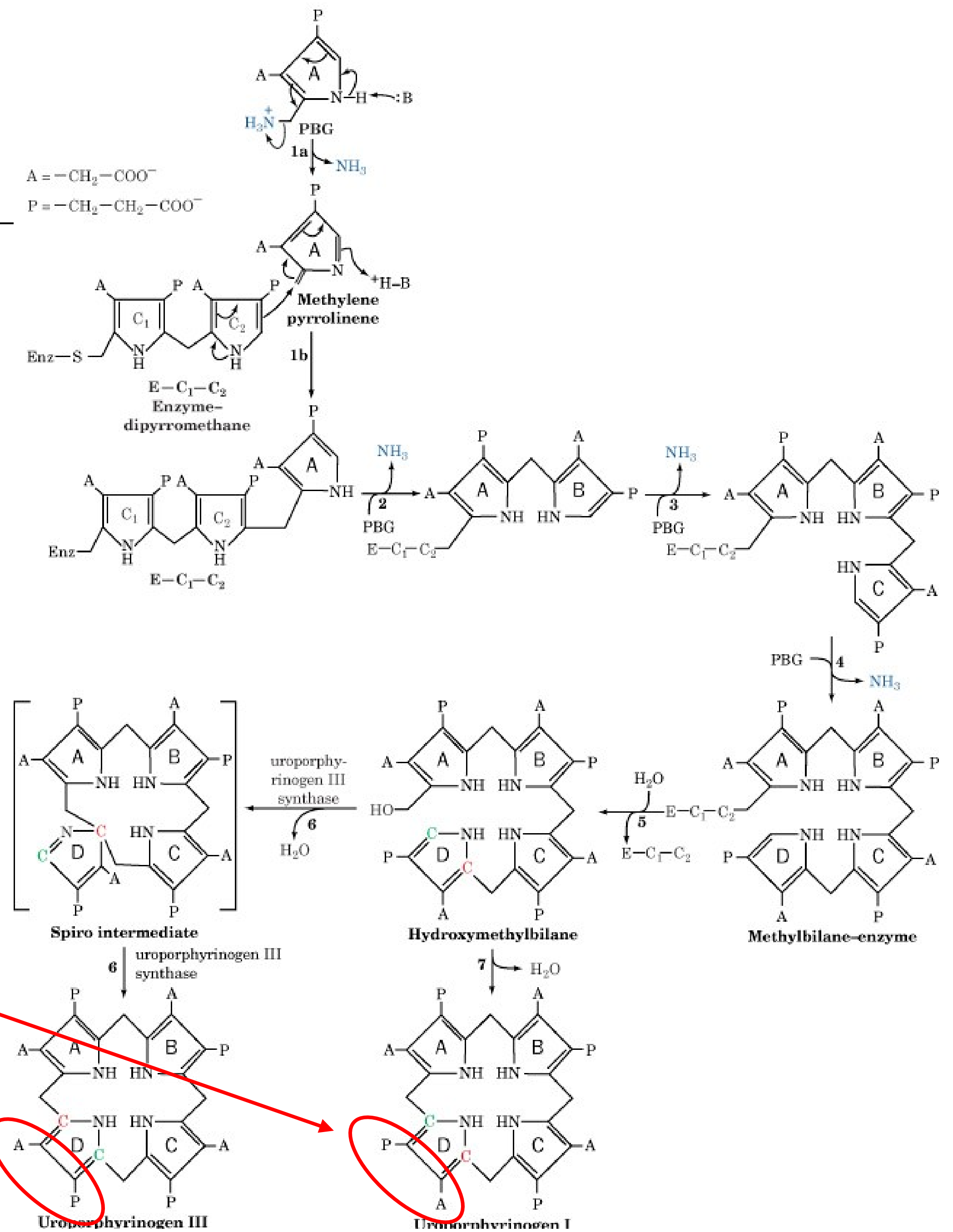
Ring close via Schiff Base



Porphyrin Synthesis from PBG

- Porphyrins are composed of 4 PBG subunits

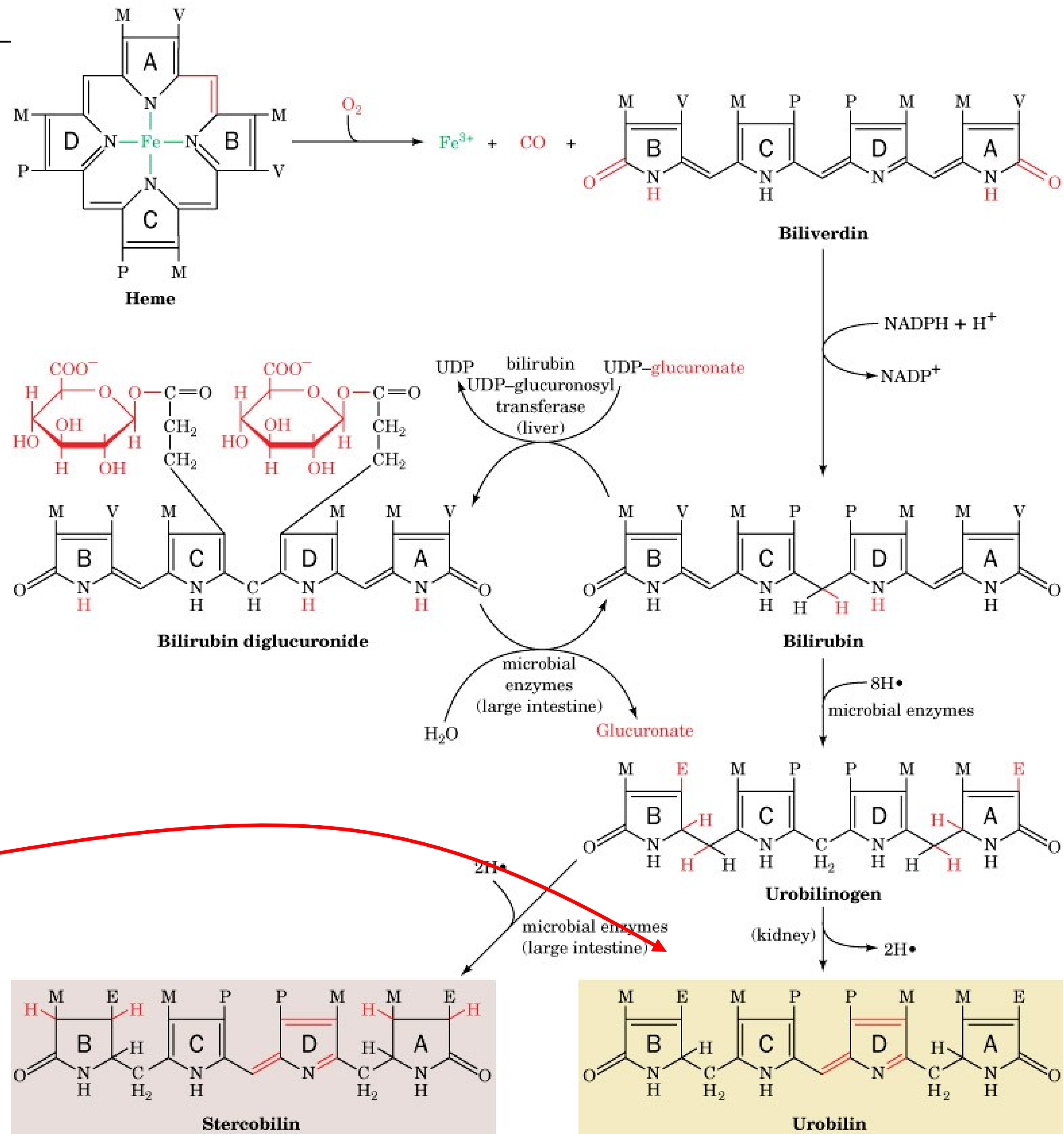
- The difference between Uroporphyrinogen I and III



Degradation of Heme

- Excreted into the large intestine in bile (from liver)

- Failure to excrete Bilirubin diglucuronide results in Bilirubin buildup in the blood, *i.e.* Jaundice.

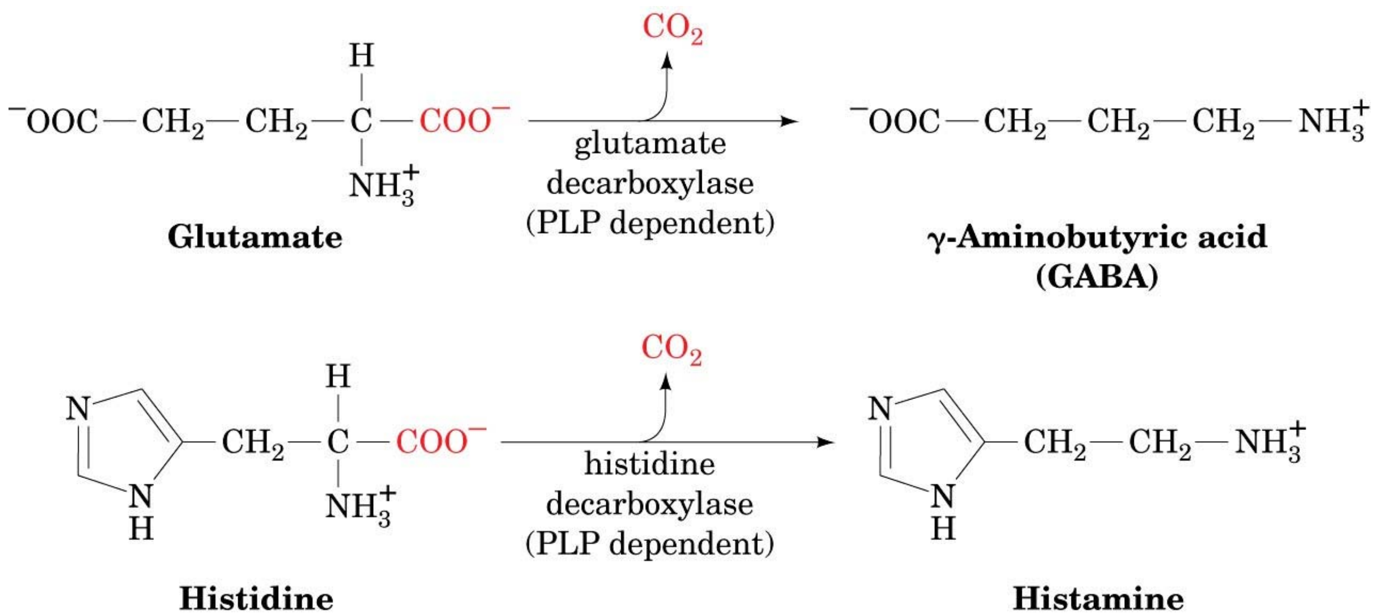


Colours pee

Colours poo

Physiologically Active Amines

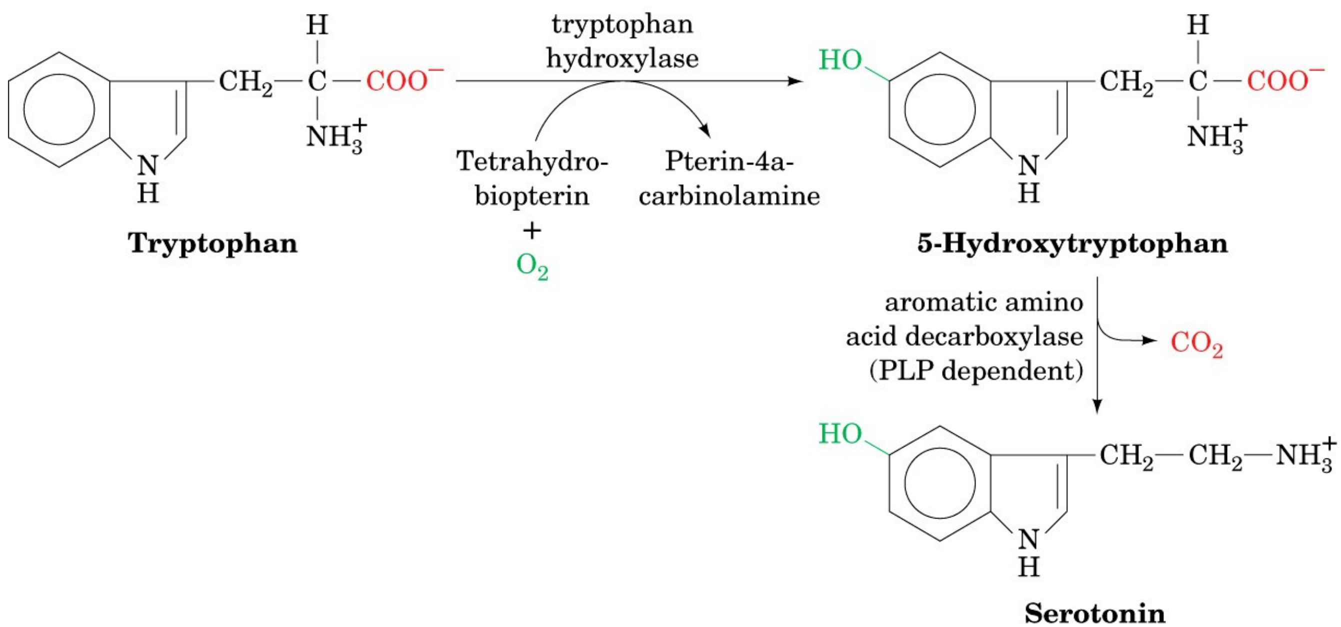
- Many signaling molecules and neurotransmitters containing amines are formed from amino acids



- GABA = very important inhibitory neurotransmitter

- Histamine = multifunctional signaling molecule (though we are most affected by immune system signaling, *i.e.* anti-histamines)

Serotonin is from Tryptophan



- Serotonin is an important neurotransmiter associated with mood (SSRIs = selective serotonin reuptake inhibitors)

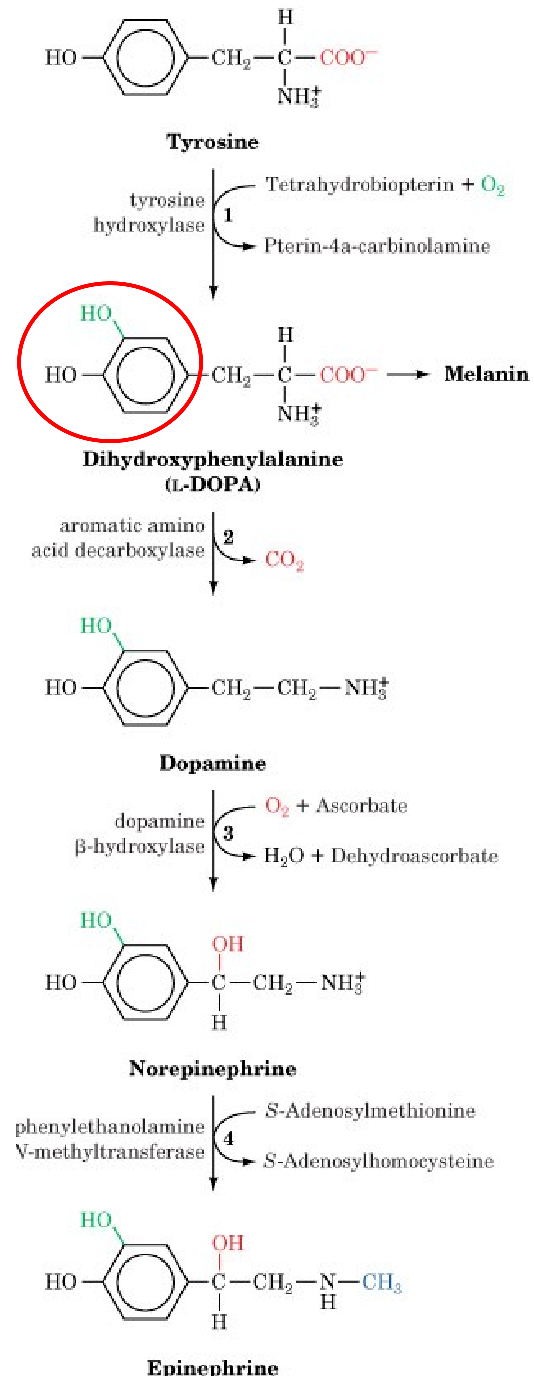
- Also important in the gut and the ‘extra sorness’ you feel when you get a cut

Catechol-based Metabolites are from Tyrosine

- Catechol-based molecules are used as hormones and neurotransmitters

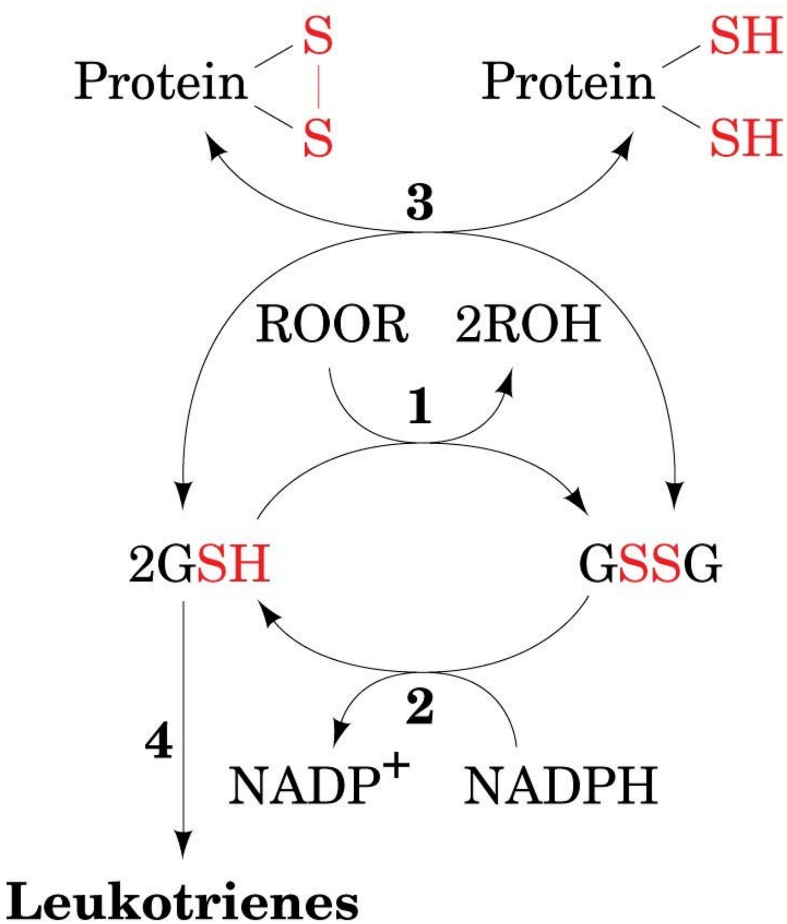
- Dopamine is associated with mood, learning, hunger etc.

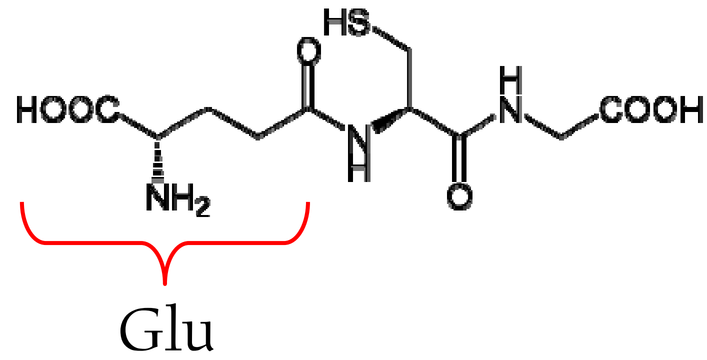
- Epinephrine is associated with getting you pumped up (*i.e.* fight or flight)



Glutathione

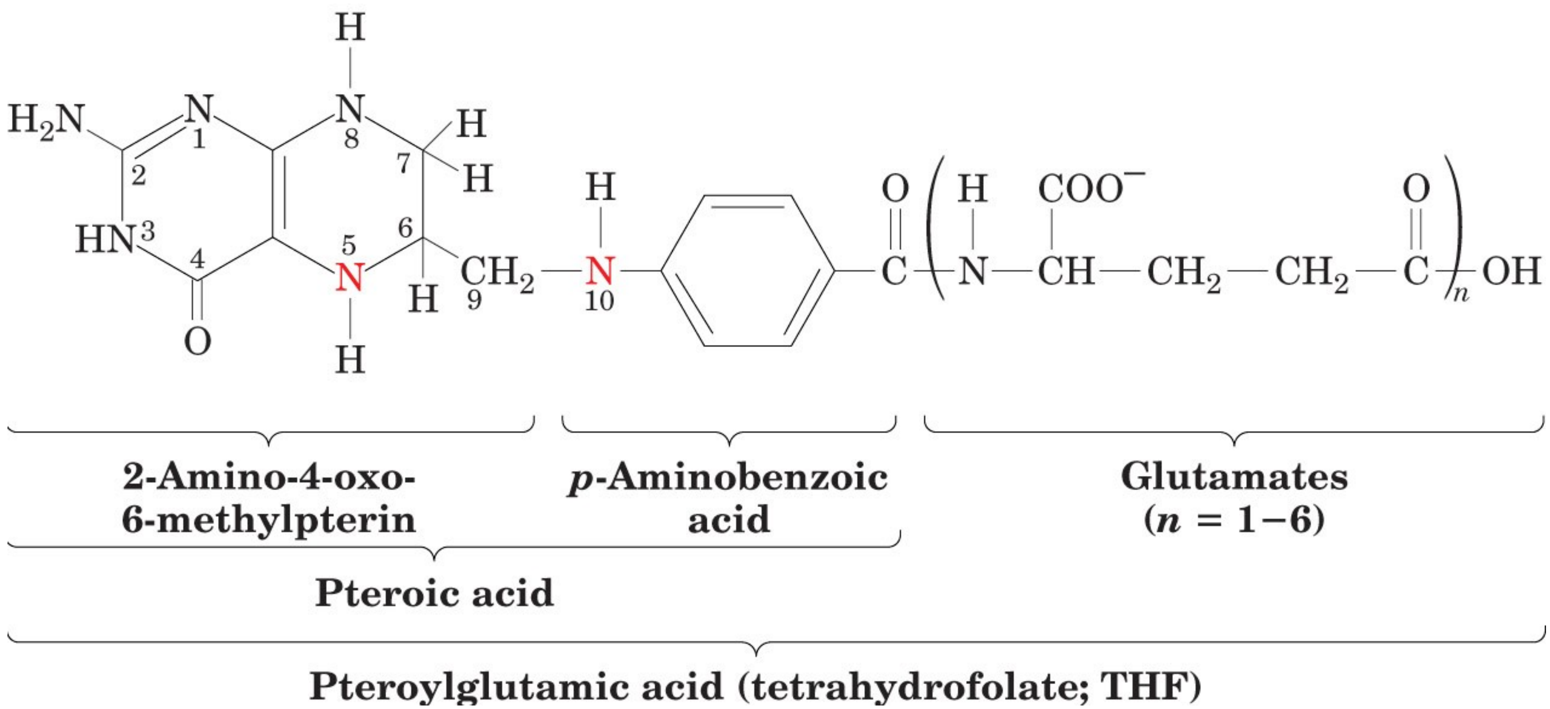
- Here's a cofactor we haven't seen yet: Glutathione (GSH) is a redox cofactor, ROS killer and keeper of the correct oxidation state for cysteines





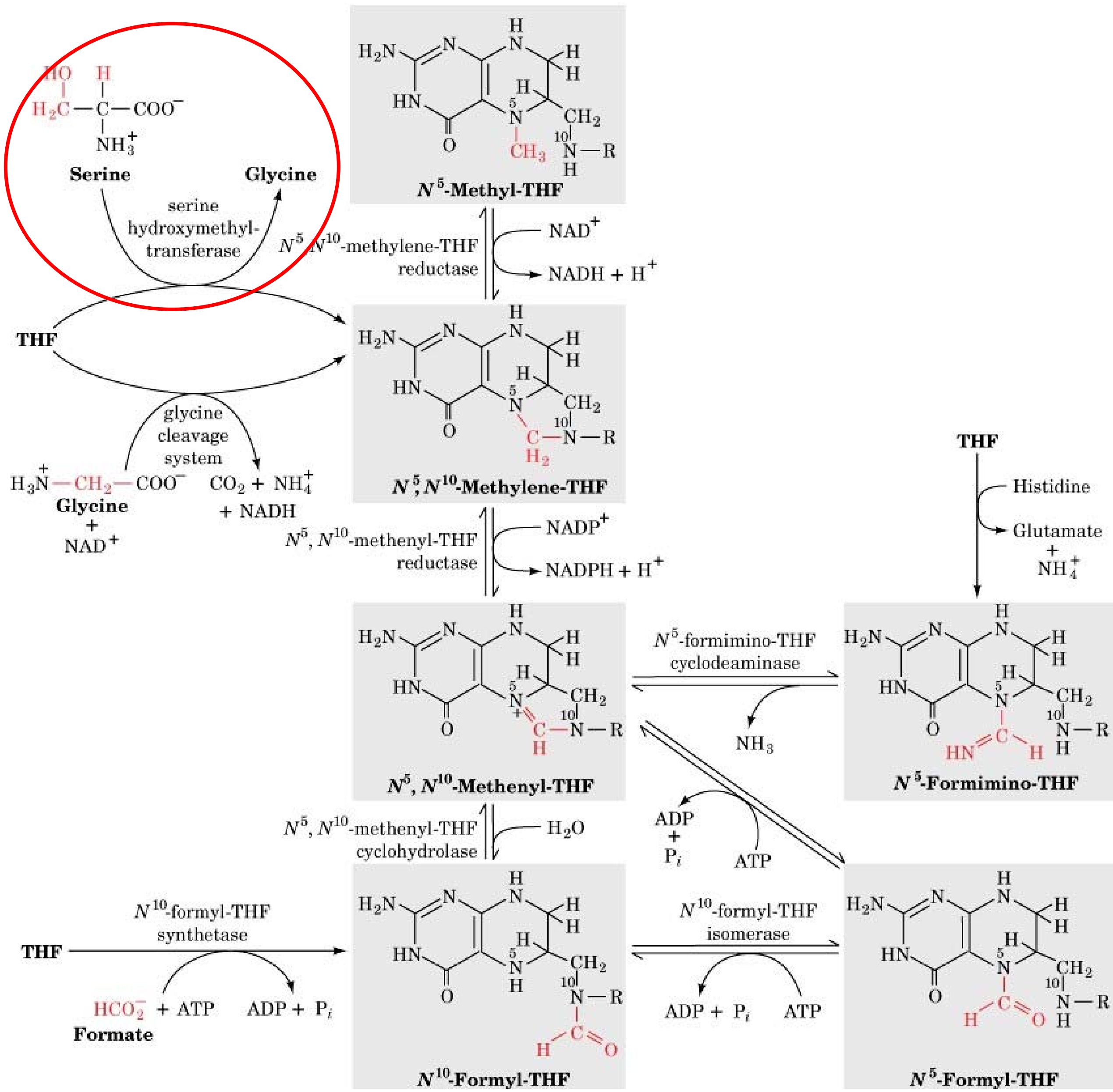
Tetrahydrofolate cofactors

- Part of the tetrahydrofolate molecule comes from a chain of condensed Glutamates



Tetrahydrofolate cofactors

- THF synthesis can be used to make Glycine from Serine



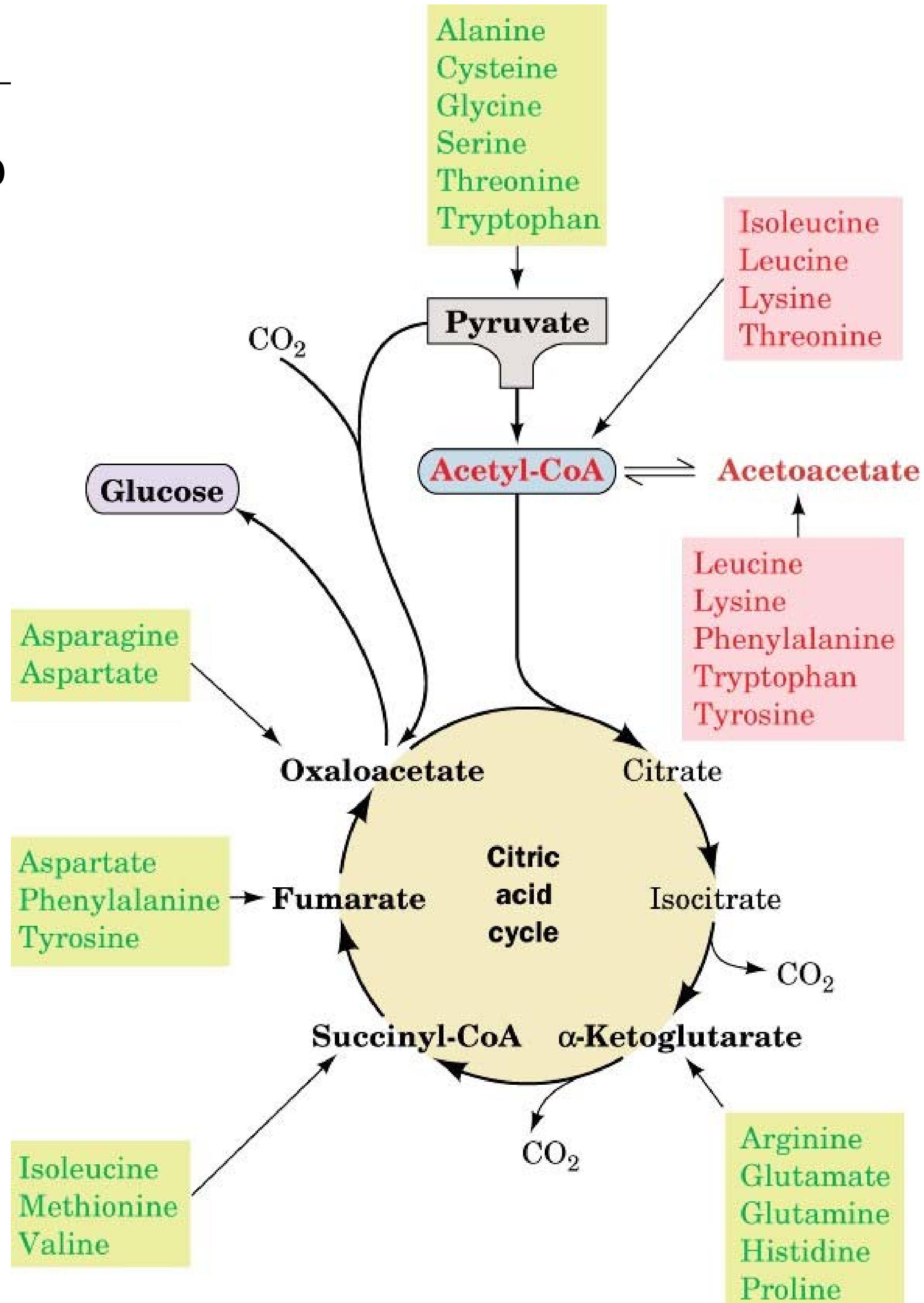
Breakdown of Amino Acids

- Here's a summary of how amino acids are broken down

- Notice that some amino acids (i.e. Leucine) are degraded to two different products.

- Amino Acids that feed intermediates in Glycolysis/ Citric Acid Cycle are Glucogenic

- Amino Acids that feed intermediates in fatty acid metabolism are Ketogenic



Pyruvate Makers

- These are broken down to Pyruvate:

Alanine

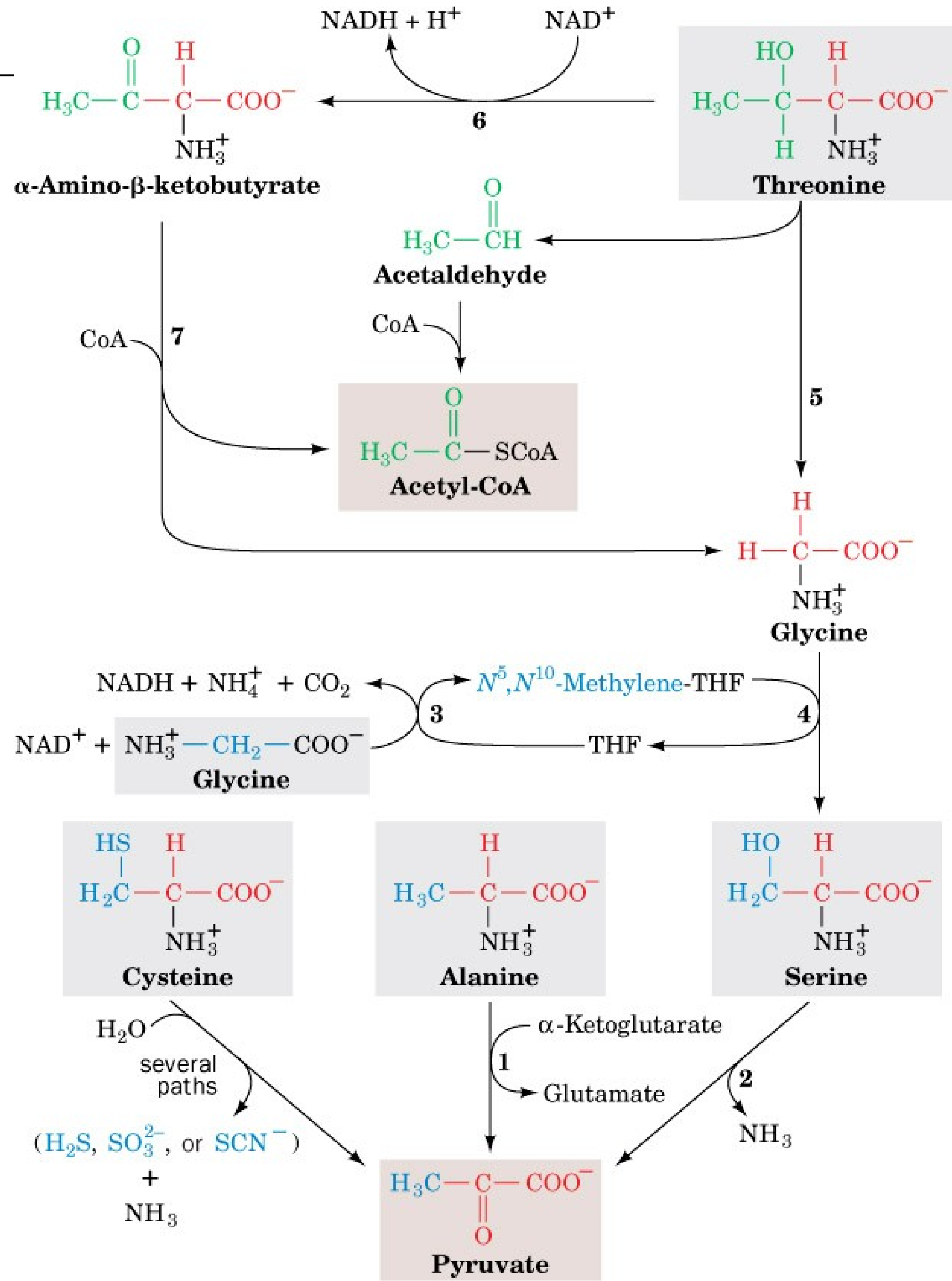
Cysteine

Glycine

Serine

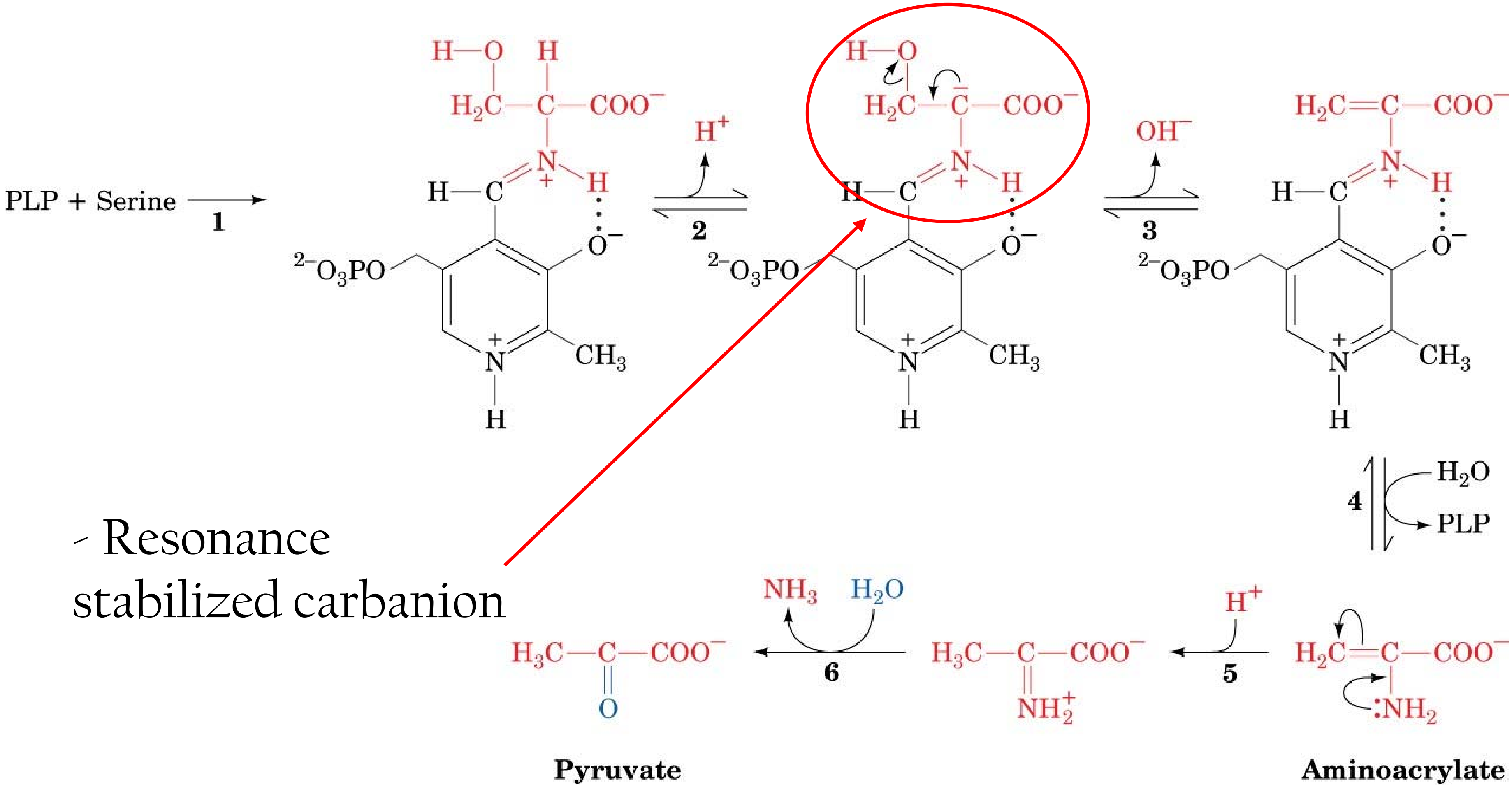
Threonine

- Of these only Alanine is made (directly) from Pyruvate



Breakdown of Serine

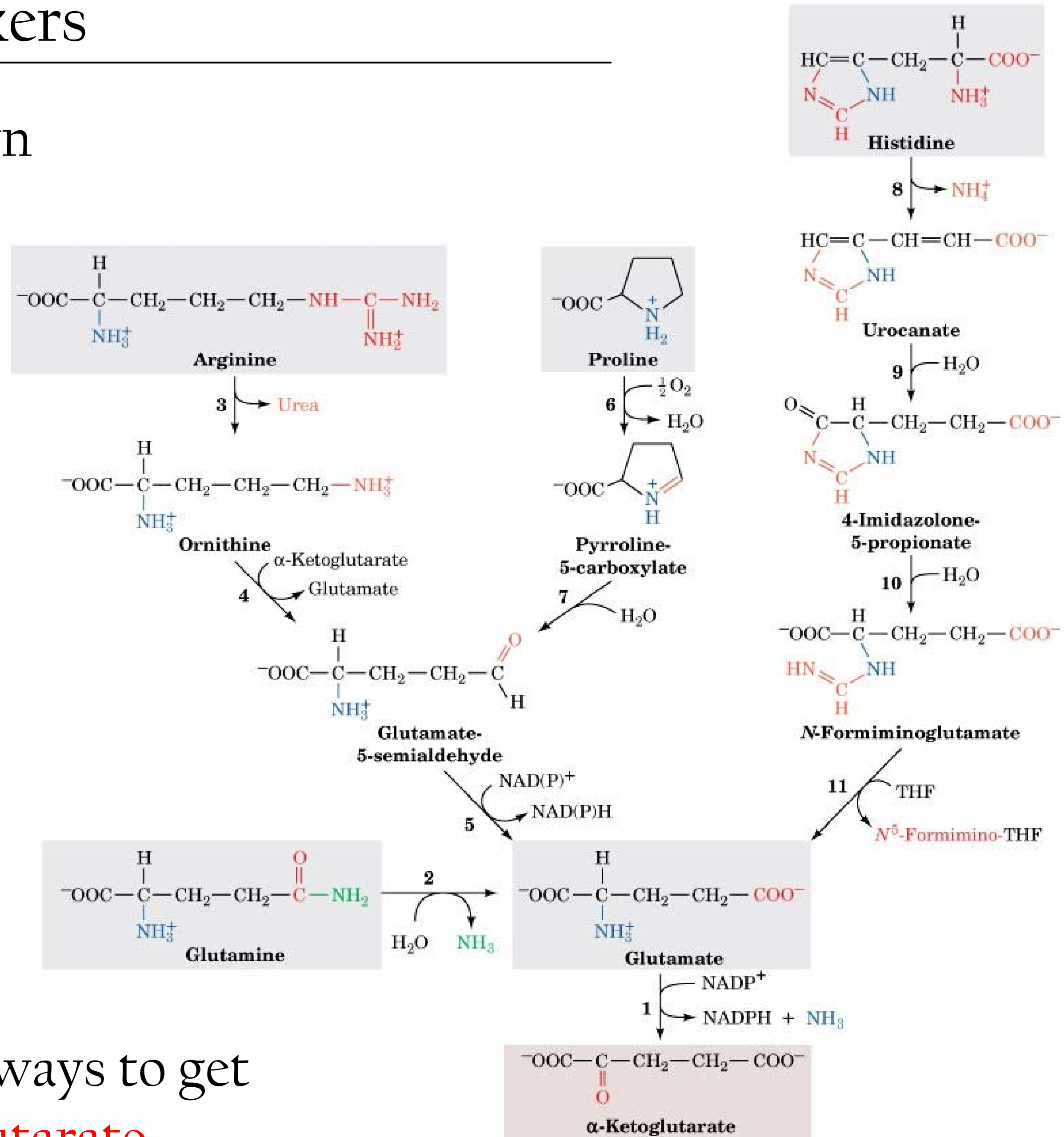
- Pyroxidal Phosphate up to it's old tricks! (see porphyrin biosyhtesis)



- Resonance stabilized carbanion

α-ketoglutarate Makers

- These are broken down into α-ketoglutarate:



Arginine

Glutamate

Glutamine

Histidine

Proline

- There are all kinds of ways to get Glutamate to α-ketoglutarate

Breakedown of Branched Chain A.A.

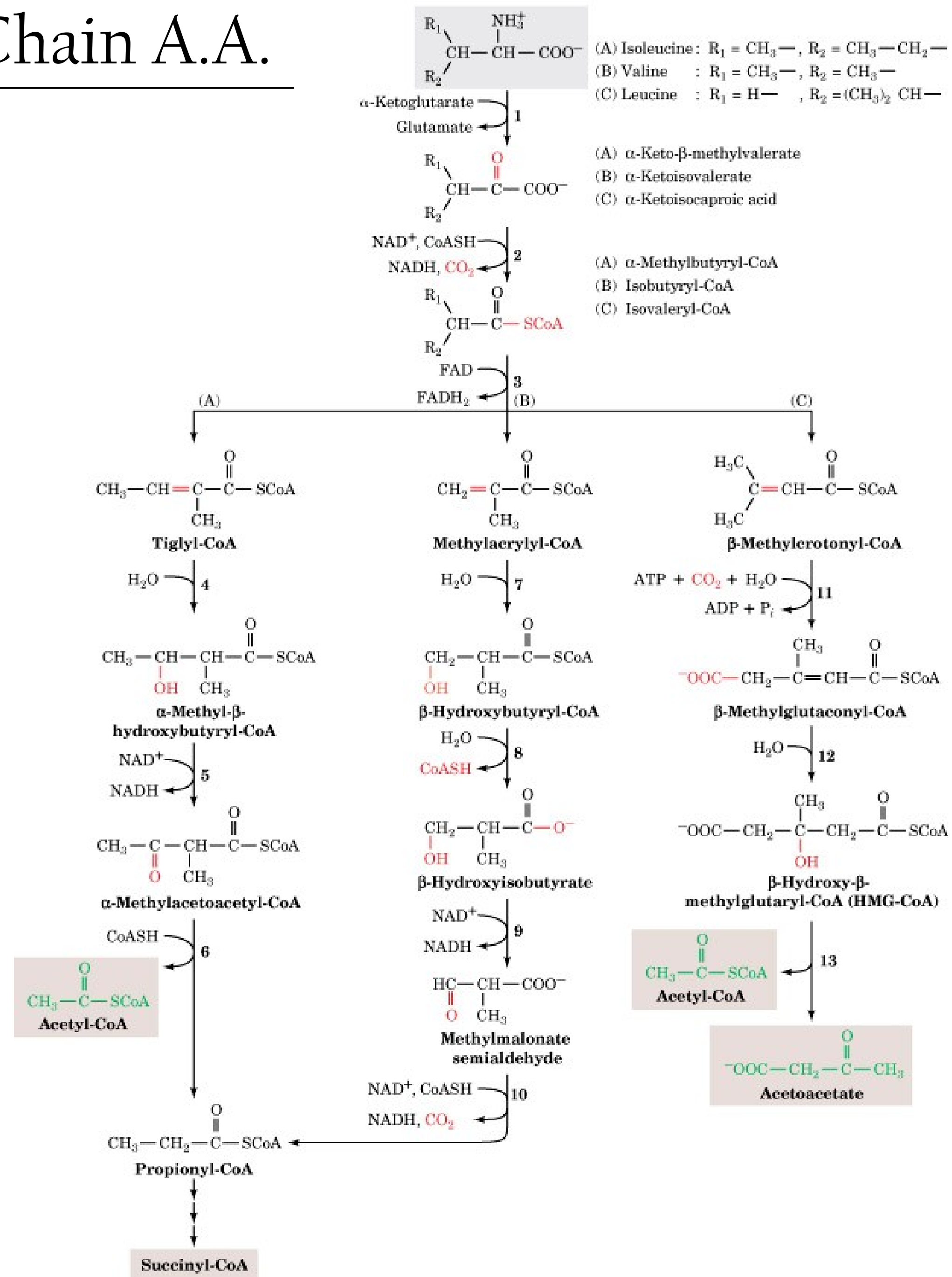
- The following make Acetyl/ Succinyl-CoA, Acetoacetate:

Isoleucine

Leucine

Valine

- Valine = 1 Succinyl-CoA
- Leucine = Acetoacetate + 1 Acetyl CoA (gluco- and keto-genic)
- Isoleucine = 1 Acetyl-CoA + 1 Succinyl-CoA

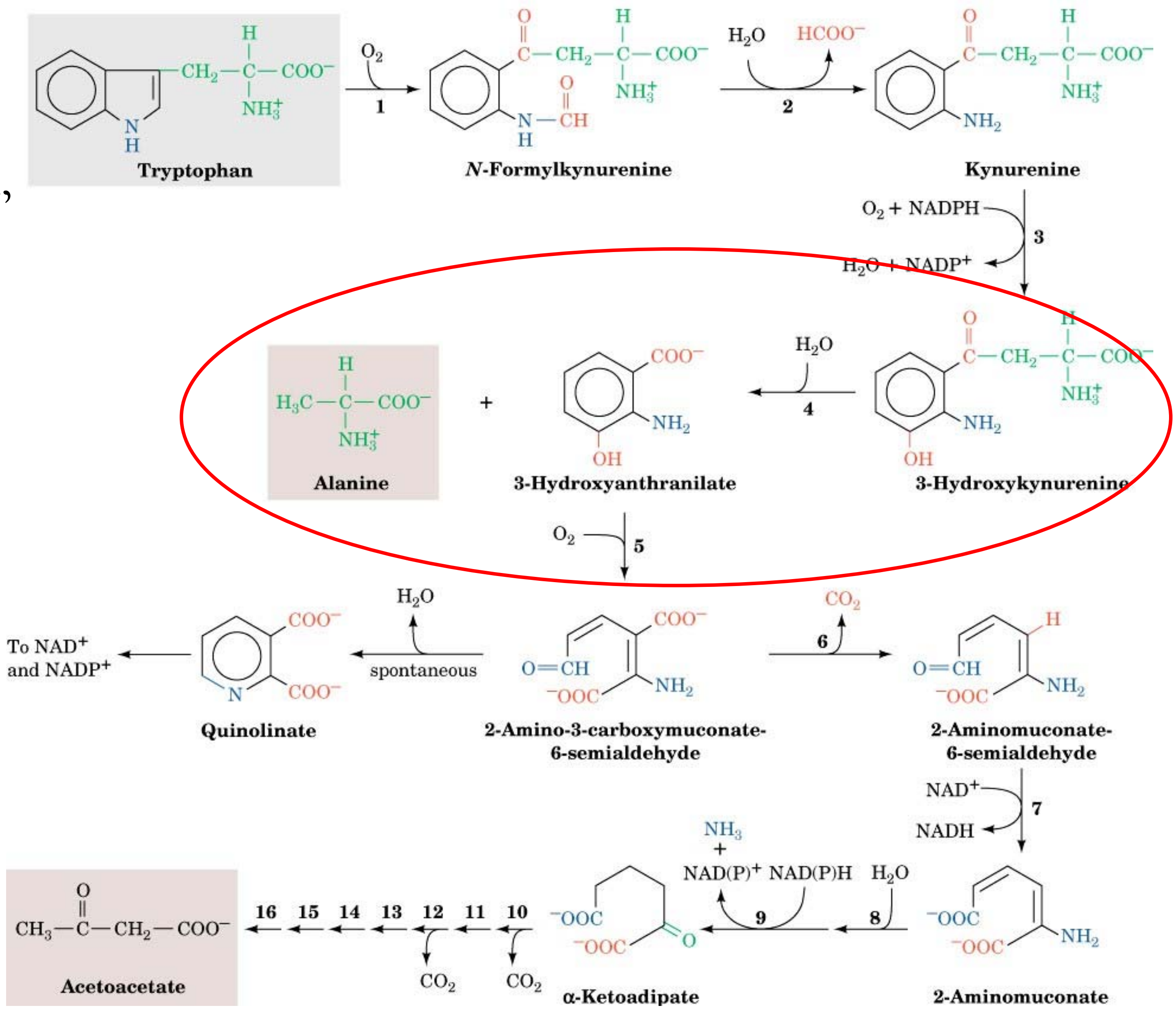


Degradation of Tryptophan

- Tryptophan is degraded by an unusual mechanism, forming Alanine in the process:

- You would think this step would involve a simple nucleophilic attack on that carbonyl carbon...

- But no!



Degradation of Tryptophan, Step 4

- This step requires… you guessed it! PLP!

- This time, PLP is used to break a C-C bond.

- This Schiff base is not acting as a Schiff base, strictly speaking. Here it is promoting the formation of a double bond.