BB 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic

Exam-1 material

Fermentations

Exam-2 material

Pyruvate
Krebs' Cycle
Oxidative Phosphorylation
Electron transport
Chemiosmotic theory: Phosphorylation

Fat Catabolism

Exam-3 material

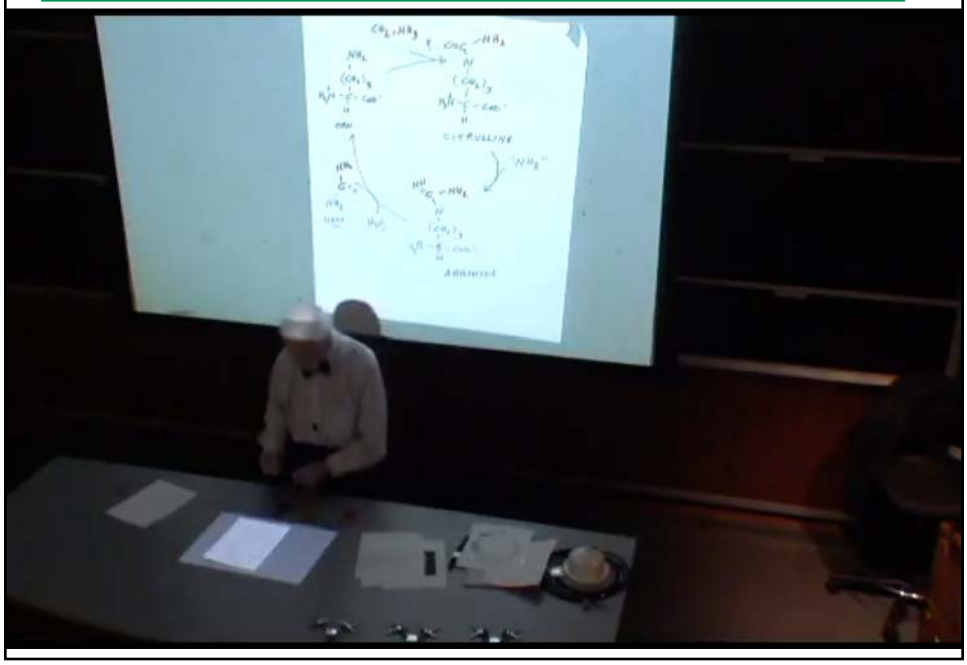
diet
storage
Fatty acid Catabolism
FOUR stages in the catabolism of lipids:
Mobilization from tissues (mostly adipose)
hormone regulated
specific lipases
glycerol
Activation of fatty acids
Fatty-acyl CoA Synthetase
Transport
carnitine
Oxidation
Rationale
Saturated FA
β-oxidation
4 steps:
dehydroge
hydration
oxidation
thiolase
energetics
Unsaturated FA
energetics
Odd-chain FA
Ketone Bodies
Other organelles

Protein Degradation (Catabolism)
Digestion
Inside of cells
Protein turnover
Ubiquitin
Proteosome
Amino-Acid Degradation
Dealing with the nitrogen
Ammonia
free
know mechanism → transamination
Carbamoyl-phosphate synthetase
Urea Cycle
5 Steps
Ornithine transcarbamylase
Arginino-succinate synthetase
Arginino-succinase
Arginase
Energetics
Urea Bi-cycle
Dealing with the carbon

Seven Families
1. ADENQ (Trans-/de- aminase Family)
2. RPH (Glu Family)
   Oxidase
   One-carbon (1-C) metabolism
   THF
   SAM
3. GSC (Pyruvate Family)
   PLP uses
4. MT – 1-C metabolism (α-KetoB Fami)
5. FY – oxidases (Aromatic Family)
6. KW (α-Ketoadipate Family)
7. VIL (Branched-chain AA Family)

Nucleic-Acid Degradation
nucleotide to bases
salvage vs oxidation
purine
pyrimidine

Amino Acid Catabolism: Urea Cycle



Amino Acid Degradation: the carbon "skeletons"

A. Concepts
   1. Convergent
   2. ketogenic/glucogenic
   3. Reactions seen before

The SEVEN (7) Families

B. Transaminase (A,D,E) / Deaminase (N,Q) Family (5)
C. Related to biosynthesis (8)
   1. Glu Family (R,P,H)
      a. Introduce oxidases/oxygenases
      b. Introduce one-carbon metabolism (1C)
   2. Pyruvate Family (G,S,C)
      a. PLP reactions
   3. α–Ketobutarate Family (M,T)
      a. 1-C metabolism
D. Dedicated (7)
   1. Aromatic Family (F,Y)
      a. oxidases/oxygenases
   2. α–Ketoadipic Family (K,W)
   3. Branched-chain Family (V,I,L)
E. Convergence with Fatty Acids: propionyl-CoA

In total there are 29 Nitrogen atoms in the 20 amino acids:
9 are given off as ammonia
18 are taken off in transaminase reactions
2 leave as urea
There are ~75 reactions in total

Amino Acid Degradation

- Intermediates of the central metabolic pathway
- Some amino acids result in more than one intermediate.
- Ketogenic amino acids can be converted to ketone bodies.

Seven to Acetyl-CoA	Leu,[7] Ile,[7] *Thr*, Lys,[6] Trp,[6] Phe,[5] Tyr[5]

NOTES:
blue bkgd=ketogenic
salmon bkgd=glucogenic
Red=both keto- and gluco-genic
Italics=different non-human pathways
Bold=pathway discussed in class

- Glucogenic amino acids can be converted to glucose.

Six to pyruvate[3,1]	Ala, *Cys*, Gly, Ser, *Thr*, Trp
Five to α-ketoglutarate[2,1]	Arg, Glu, Gln, His, Pro
Four to succinyl-CoA[7,4]	Ile, Met, **Thr**, Val
Two to fumarate[5]	Phe, Tyr
Two to oxaloacetate[1]	Asp, Asn

[1]Trans-/de-aminase family
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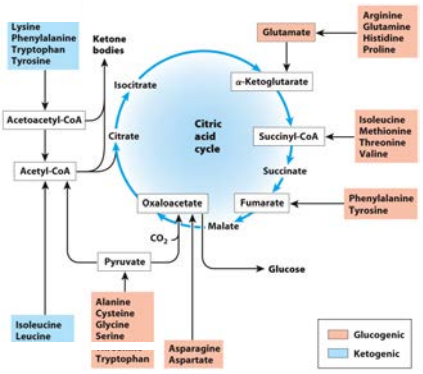
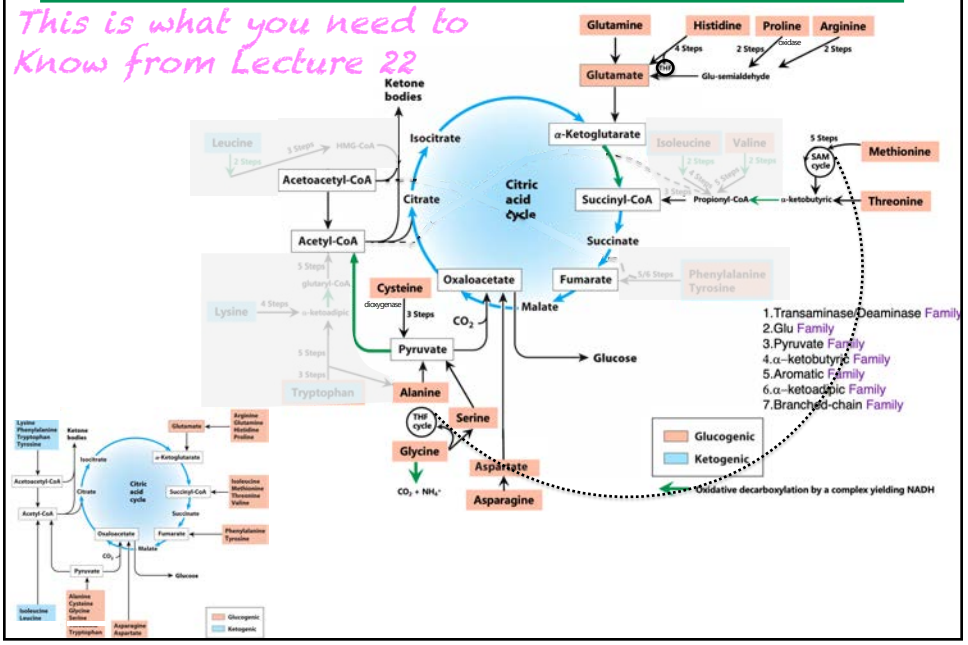


Amino Acid Degradation

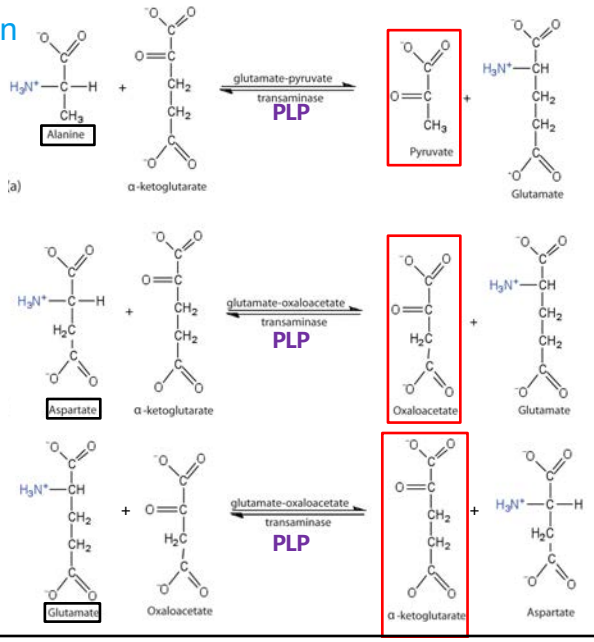
This is what you need to Know from Lecture 22



Amino Acid Degradation

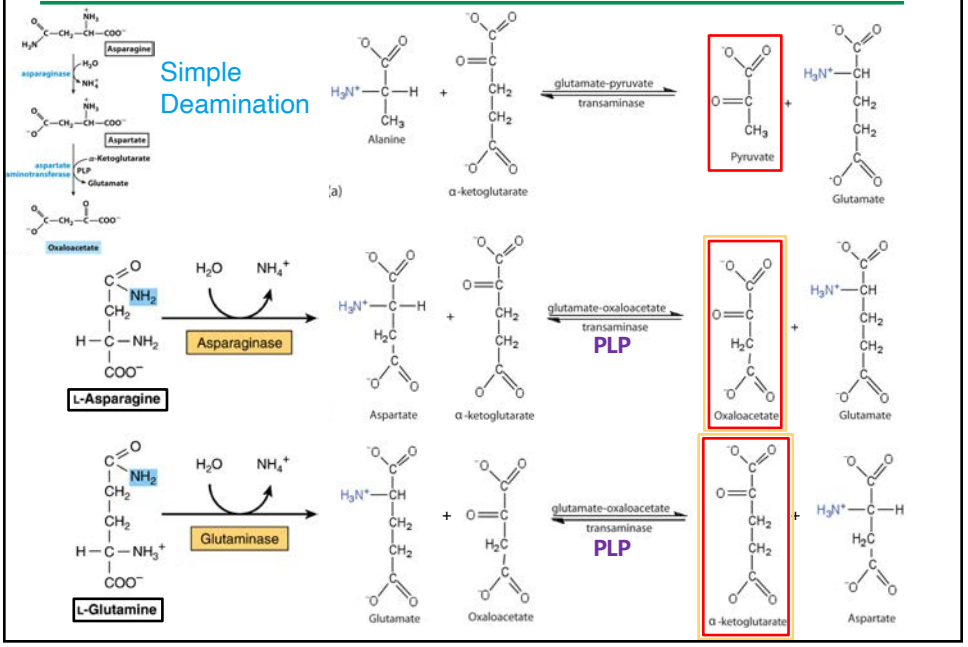
A,D,E

Simple Transamination



Amino Acid Degradation

N,Q



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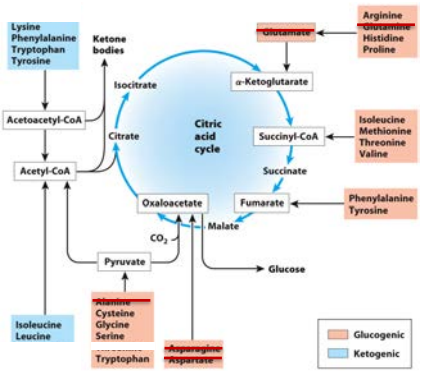
Two to oxaloacetate[1]



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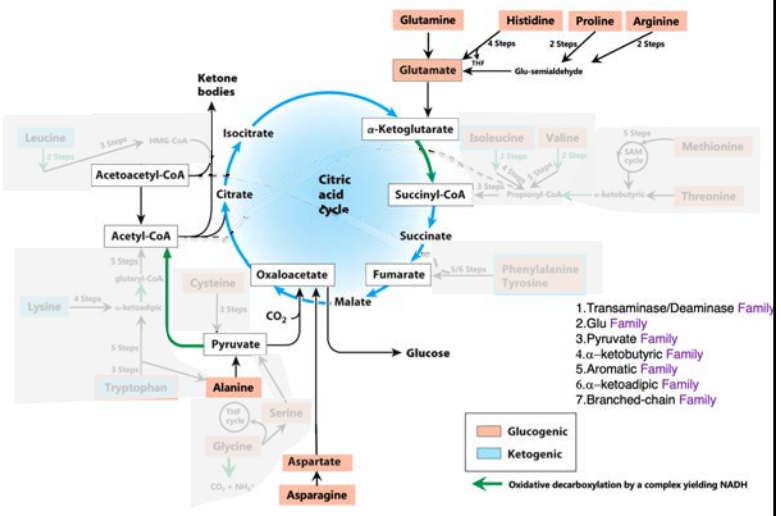
Before Glu

Amino Acid Degradation

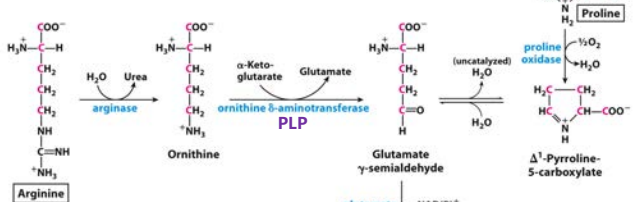


Amino Acid Degradation

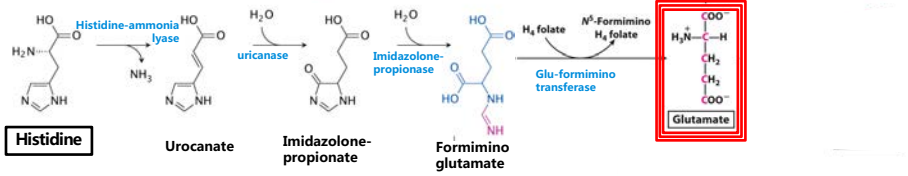
R,P,H

Glu Family

Arginine degradation is part of the urea cycle.

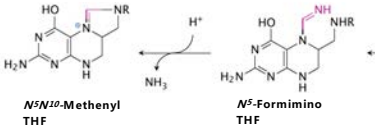


Proline, arginine, and histidine are all converted to glutamate.

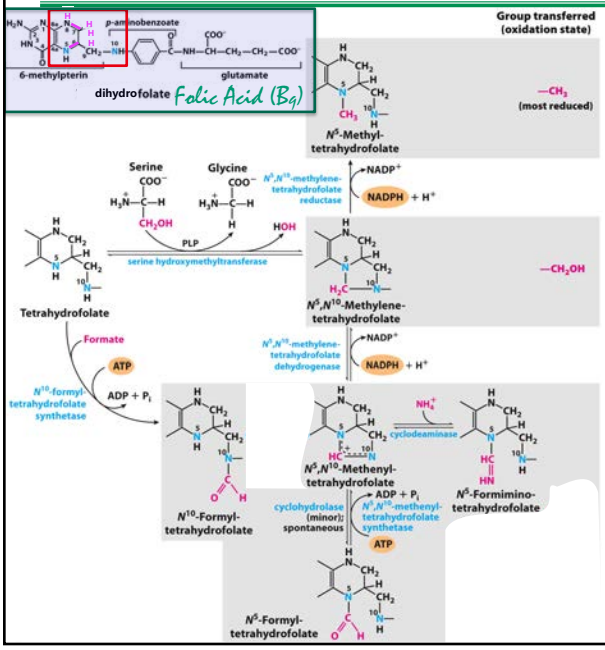


Three new metabolic concepts used:

1) Other uses of PLP
2) Oxidases & oxygenases
3) One-carbon metabolism



Amino Acid Degradation: One Carbon

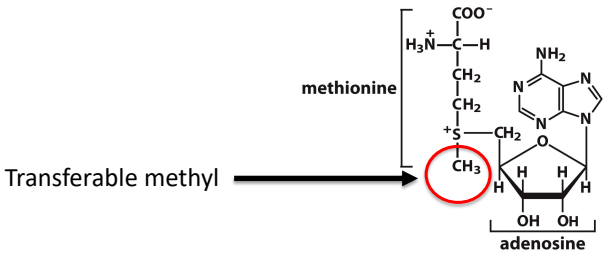


- Tetrahydrofolate is formed from folate.
  - an essential vitamin
  - Folate is reduced to dihydrofolate, then to tetrahydrofolate (THF)
- It is used in a wide variety of metabolic reactions.
- THF can transfer 1-carbon in different oxidation states.
  - CH_3, CH_2OH, and CHO
- Carbon generally comes from serine.
- Forms are interconverted on THF before use.

The other half of one-carbon metabolism is SAM, which is connected to N^5-methyl-THF

Amino Acid Degradation: One Carbon

S-Adenosyl-Methionine (SAM or adoMet)

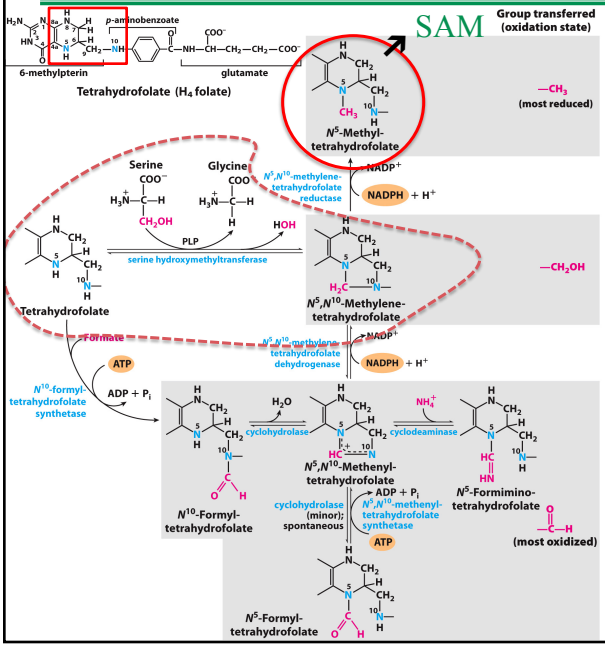


***S*-Adenosylmethionine (adoMet)**

SAM is Better at Transferring CH_3

- *S*-adenosylmethionine is the preferred cofactor for methyl transfer in biological reactions.
  - Methyl in SAM is 1000 times more reactive than THF-methyl group.
- It is synthesized from ATP and methionine in the "SAM Cycle" (part of α-ketobutyrate family (M,T))
- Regeneration of SAM uses N^5-methyl THF.
  - The only known use of N^5-methyl THF in mammals

Amino Acid Degradation: One Carbon



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We'll come back to 1-C metabolism when we see what happens to Met

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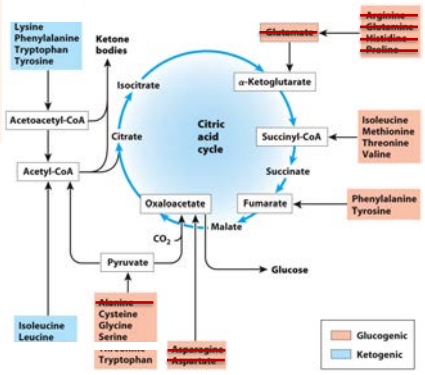

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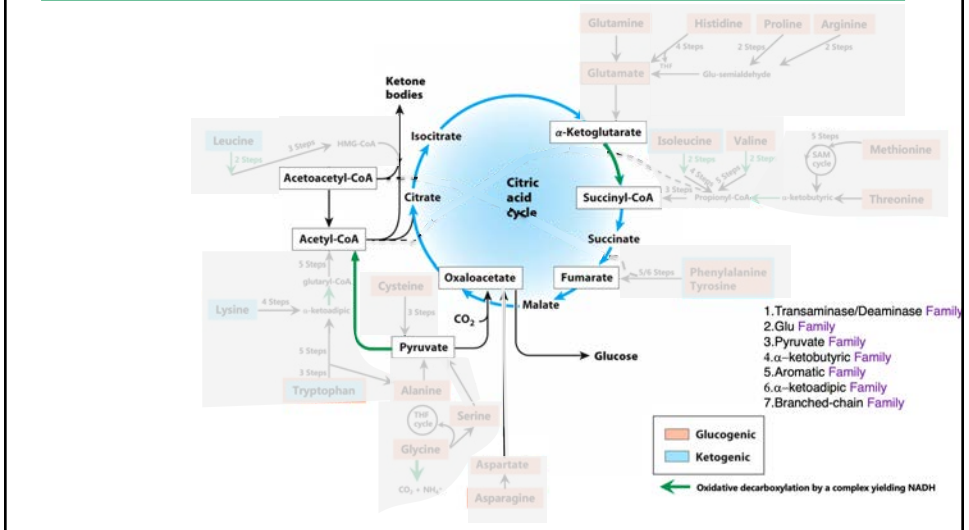
Amino Acid Degradation

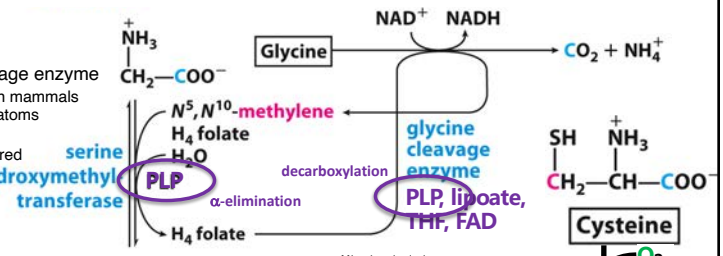


Amino Acid Degradation

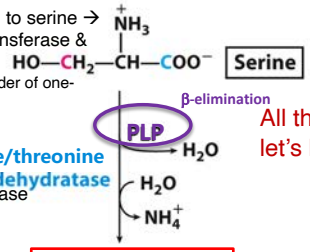
G,S,C

Pyruvate Family
Glycine

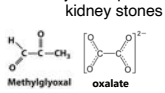
- Pathway #1: glycine cleavage enzyme
  - apparently major pathway in mammals
  - separation of three central atoms
  - releases CO_2 and NH_3
  - methylene group is transferred to THF
  - mechanism like PDH complex



- Pathway #2: hydroxylation to serine → pyruvate via SerOHMe transferase & Set/Thr dehydratase
  - Reverse reaction major feeder of one-carbon to THF

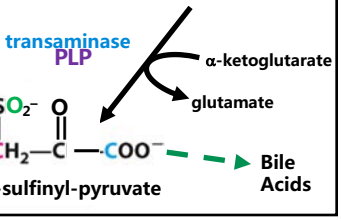


- Pathway #3: D-amino oxidase
  - relatively minor pathway
  - ultimately oxidized to oxalate
  - major component of kidney stones



Microbes hydrolyze H_2S & ammonia with desulfhydrase or TA then SH→SCN

All these uses of PLP; let's have a closer look

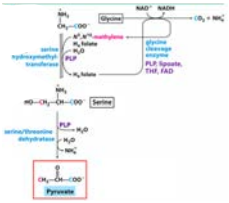


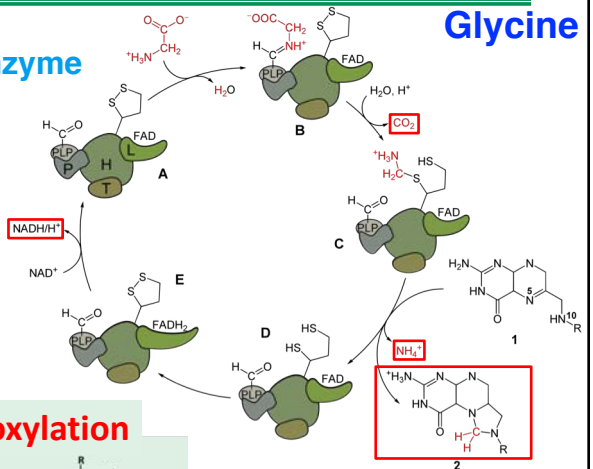
Amino Acid Degradation G,S,C

Pyruvate Family: Glycine

Glycine Cleavage Enzyme

See *Achieve* animated Figures

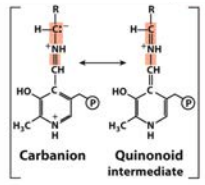




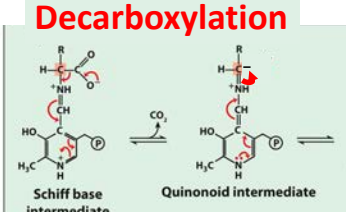
N^5-N^{10}-methylene-THF

This is similar to how THF was used to pick off the form-imino group in His catabolism

Decarboxylation



Resonance structures for stabilization of a carbanion by PLP



In Photosynthetic Parts of Plants, this is one of the most Abundant proteins and its called Glycine Decarboxylase

http://media.saplinglearning.com/priv/he/lehninger/aem/1820c_glycine_cleavage.html

Mechanism of Glycine Decarboxylase

- In plants, this same ortholog of Gly-clevage enzyme is called Gly decarboxylase
- Flux through rubisco reaction and glycolate pathway can be high in bright sun, so plants need a lot of glycine decarboxylase.
  - makes up 50% of protein in some plant leaves
  - but non-photosynthetic parts of plants (tubers, etc.) have *little* glycine decarboxylase

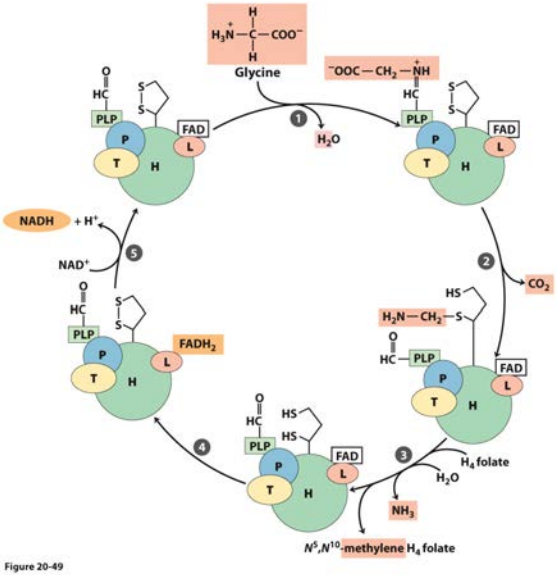


Figure 20-49

Glycine Decarboxylase Is Abundant in Photosynthetic Parts of Plants

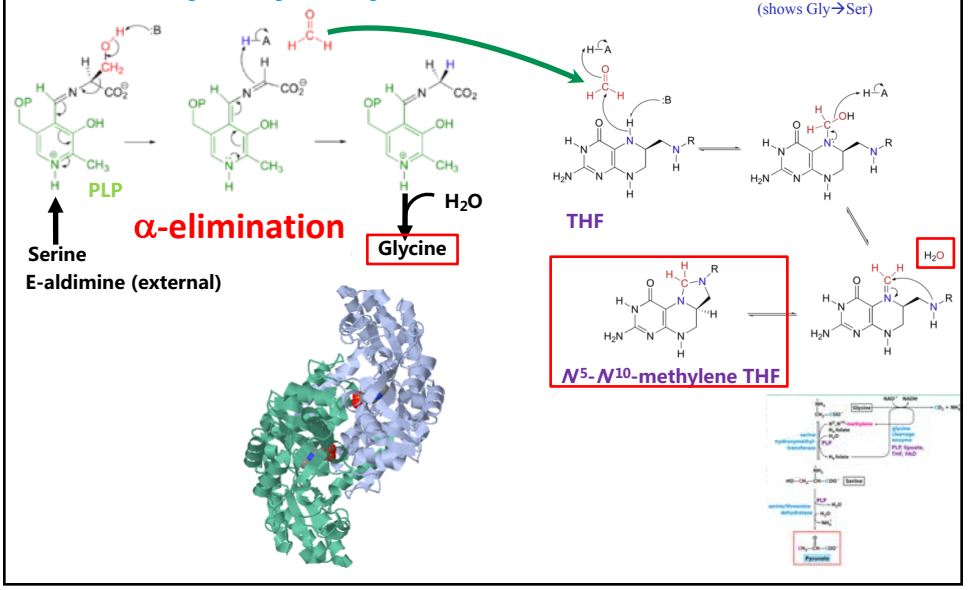
Amino Acid Degradation G,S,C

Pyruvate Family:

Serine hydroxymethyl transferase

Serine/Glycine

See Sapling animated Figure (shows Gly→Ser)



Amino Acid Degradation G,S,C

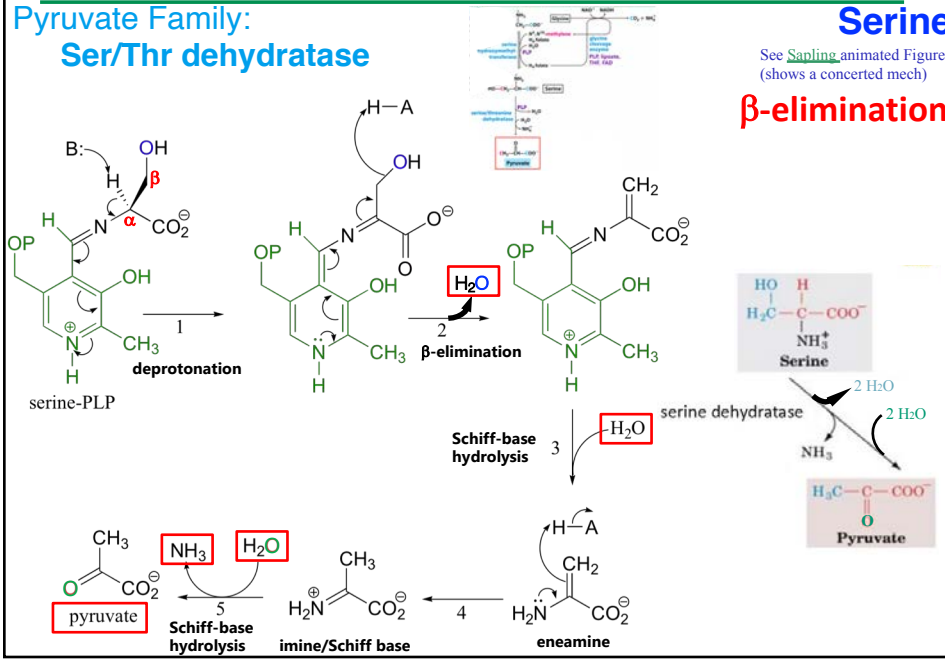
Pyruvate Family:

Ser/Thr dehydratase

Serine

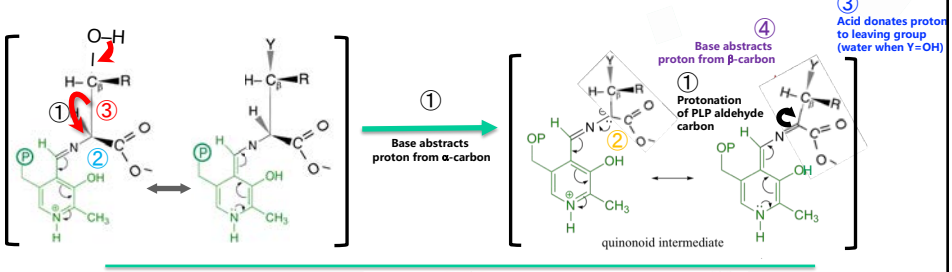
See Sapling animated Figures (shows a concerted mech)

β-elimination



Amino Acid Degradation

PLP Catalyzes Many Types of Reactions

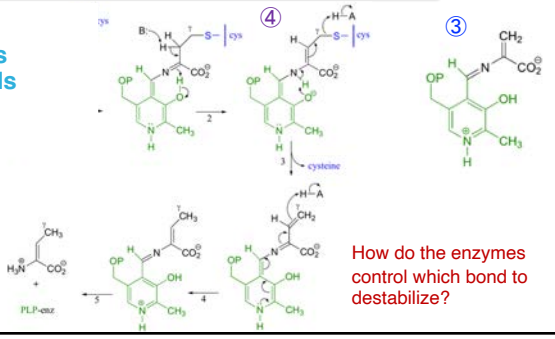


Cα-bond:

① Transamination of Amino Acids
② Decarboxylation of Amino Acids
③ α-elimination of Amino Acids

After Cα-H abstracted ① :

② Racemization of Amino Acids
③ β-elimination of Amino Acids
④ γ-elimination of Amino Acids



How do the enzymes control which bond to destabilize?

Amino Acid Degradation

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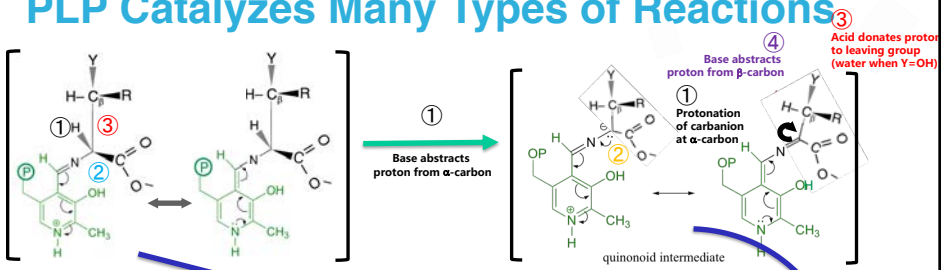

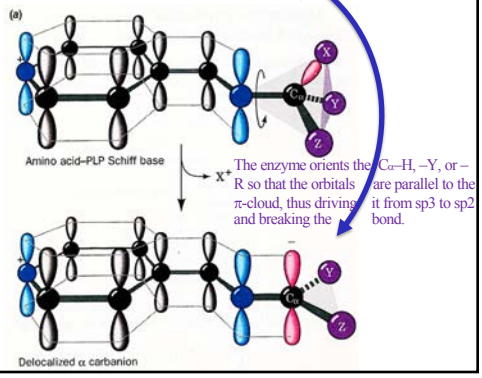

The enzyme orients the Cα–H, –Y, or –R so that the orbitals are parallel to the π-cloud, thus driving it from sp3 to sp2 and breaking the bond.

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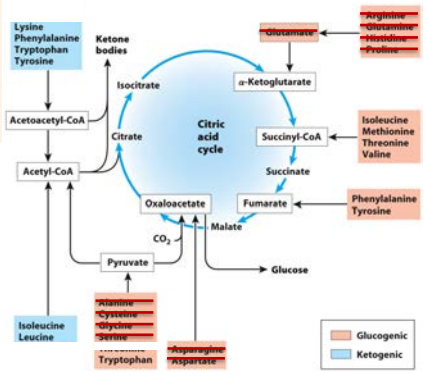

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A. Concepts
1. Convergent
2. ketogenic/glucogenic
3. Reactions seen before

The SEVEN (7) Families

B. Transaminase (A,D,E) / Deaminase (Q,N) Family
C. Related to biosynthesis (8)
1. Glu Family (R,P,H)
a. Introduce oxidases/oxygenases
b. Introduce one-carbon metabolism (1C)
2. Pyruvate Family (G,S,C)
a. PLP reactions
3. α–Ketobutyric Family (M,T)
a. 1-C metabolism
D. Dedicated (7)
1. Aromatic Family (F,Y)
a. oxidases/oxygenases
2. α–Ketoadipic Family (K,W)
3. Branched-chain Family (V,I,L)
E. Convergence with Fatty Acids: propionyl-CoA

Before MT