BI/CH 422/622

OUTLINE:

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

Exam-1 material

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

Exam-2 material

Fat Catabolism
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:
dehydrogenation
hydration
oxidation
thiolase
energetics
Unsaturated FA
energetics
Odd-chain FA
Ketone Bodies
Other organelles

Exam-3 material

Protein Degradation (Catabolism)
Digestion
Inside of cells
Protein turnover
Ubiquitin
Proteosome
Amino-Acid Degradation
Dealing with the nitrogen
Ammonia
free
transamination ← know mechanism
Carbamoyl-phosphate synthetase
Urea Cycle
4 Steps
Ornithine transcarbamylase
Arginino-succinate synthetase
Arginino-succinase
Arginase
Energetics
Urea Bi-cycle
Dealing with the carbon
Seven Families
1. ADENQ (Transaminase/deaminase 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-Ketobutyrate Family)
5. FY – oxidases (Aromatic Family)
6. KW (α-Ketoadipate Family)
7. VIL (Branched-chain AA Family (BCAA))

Fates of the 29 nitrogen atoms in 20 AA:

9 ammonia
18 transamination
2 urea

Amino Acid Degradation

G,S,C

- 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]

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Five to α-ketoglutarate[2,1]
Four to succinyl-CoA[7,4]: Ile, Met, **Thr**, Val
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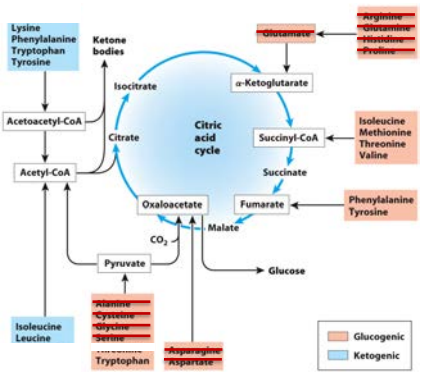

Amino Acid Degradation: the carbon "skeletons"

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

The SEVEN (7) Families

B. Transaminase (A,D,E) / Deaminase (Q,N) Family
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D. Dedicated (7)
   1. Aromatic Family (F,Y)
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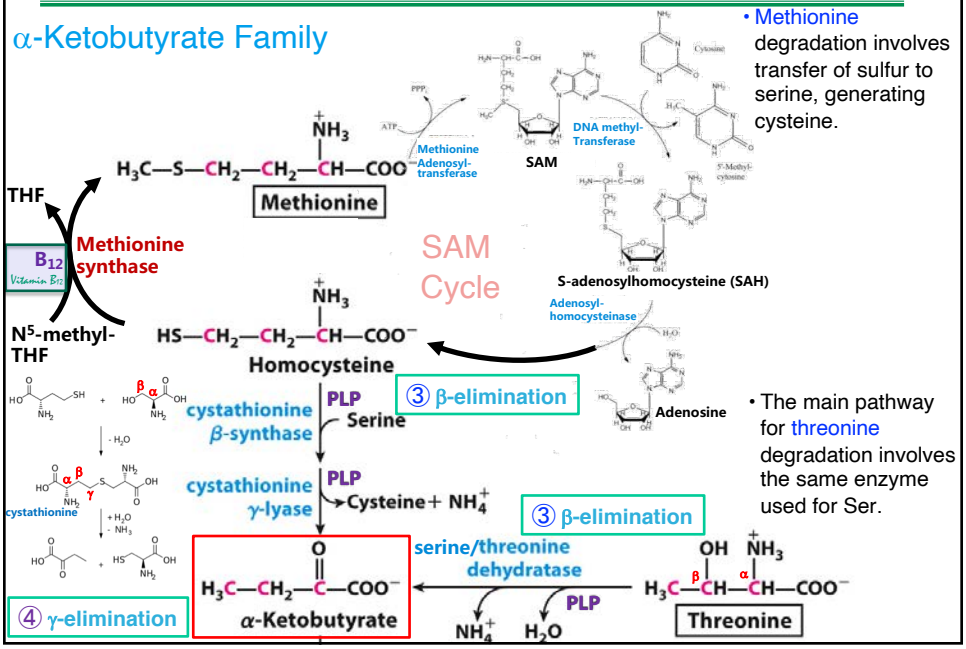
   2. α–Ketoadipic Family (K,W)
   3. Branched-chain Family (V,I,L)
E. Convergence with Fatty Acids: propionyl-CoA

Before MT

Amino Acid Degradation

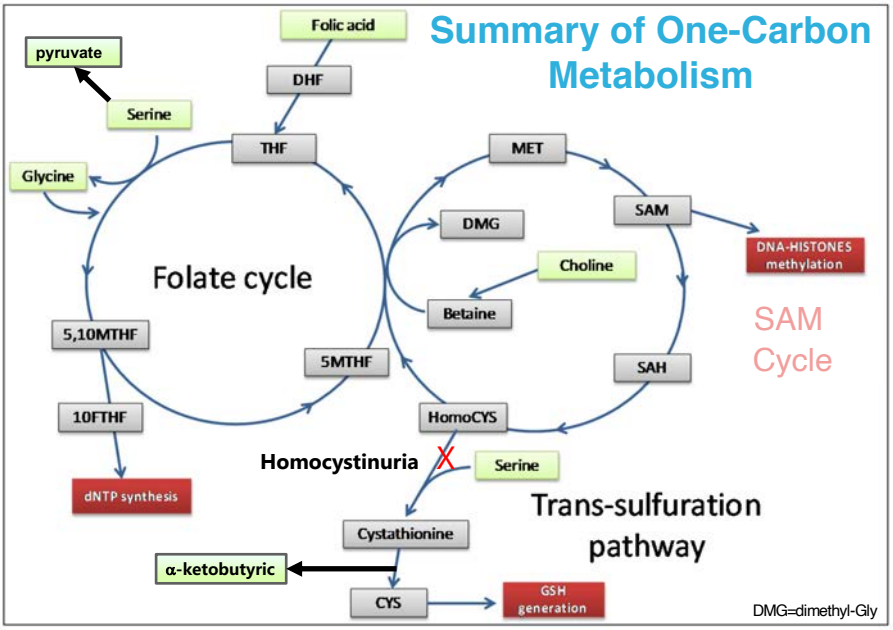
M,T

α-Ketobutyrate Family



- Methionine degradation involves transfer of sulfur to serine, generating cysteine.
- The main pathway for threonine degradation involves the same enzyme used for Ser.

Amino Acid Degradation: One Carbon



Amino Acid Degradation

M,T

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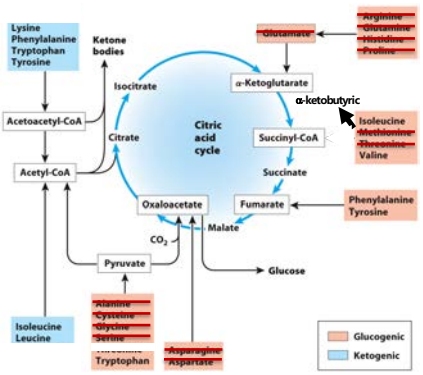

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   1. Aromatic Family (F,Y)
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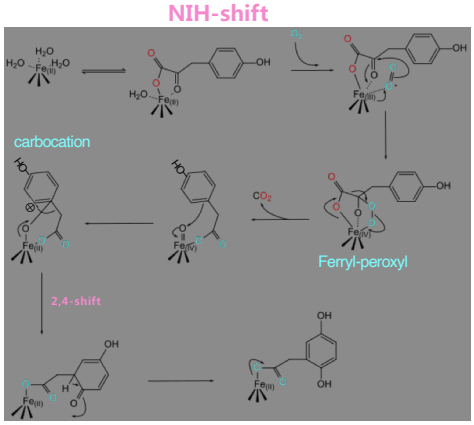
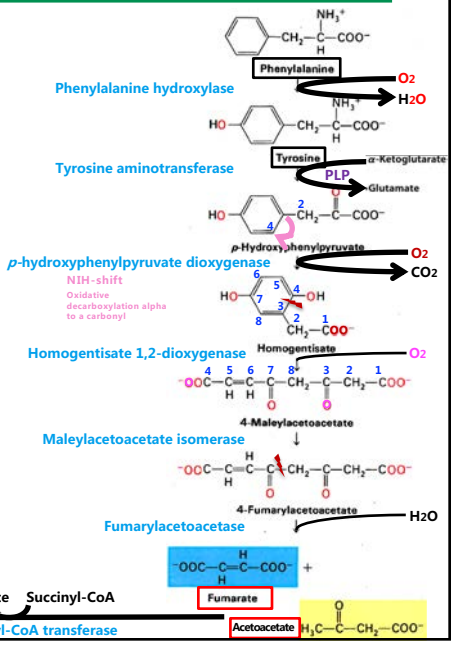
Before FY

Amino Acid Degradation

F,Y

Aromatic Family

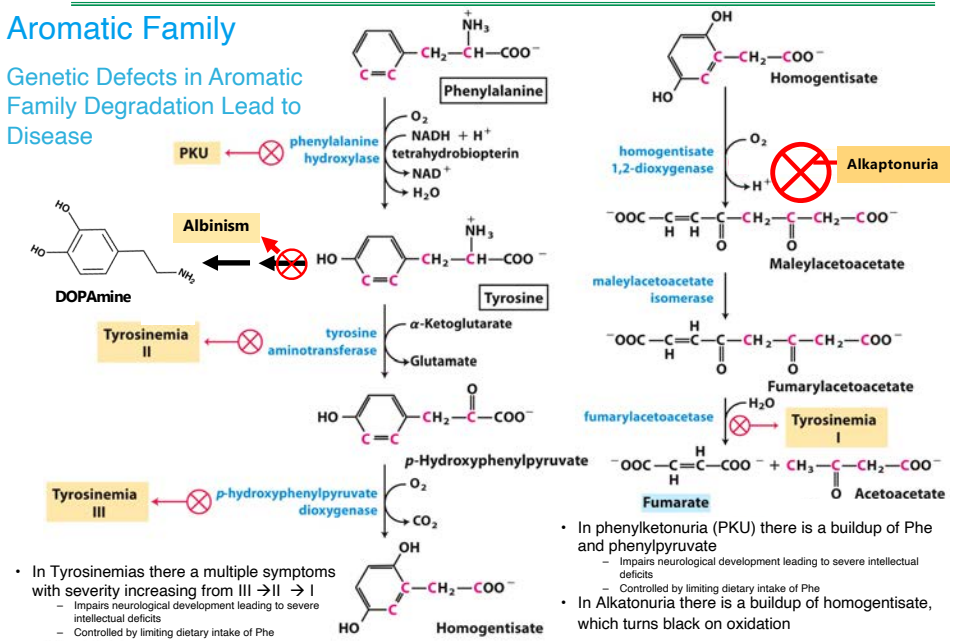




Amino Acid Degradation

Aromatic Family

Genetic Defects in Aromatic Family Degradation Lead to Disease



- In Tyrosinemias there a multiple symptoms with severity increasing from III →II → I
  - Impairs neurological development leading to severe intellectual deficits
  - Controlled by limiting dietary intake of Phe
- In phenylketonuria (PKU) there is a buildup of Phe and phenylpyruvate
  - Impairs neurological development leading to severe intellectual deficits
  - Controlled by limiting dietary intake of Phe
- In Alkatonuria there is a buildup of homogentisate, which turns black on oxidation

Amino Acid Degradation: Oxidases

Nomenclature

Oxidases – use molecular oxygen as an electron acceptor, but no atoms into substrate

- e.g., cytochrome oxidase, proline oxidase
- usually have water or hydrogen peroxide as product

$$A(red) + O_2 + 4H^+ \rightarrow A(ox) + 2H_2O$$

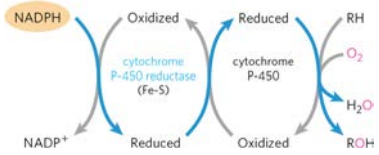
Oxygenase* – use of molecular oxygen to put into the substrate

- dioxygenases – use both atoms; e.g., cysteine dioxygenase

$$A + O_2 \rightarrow AO_2$$

- mono-oxygenases – one atom in substrate, one atom as water

$$RH + BH_2 + O_2 \rightarrow ROH + B + H_2O$$



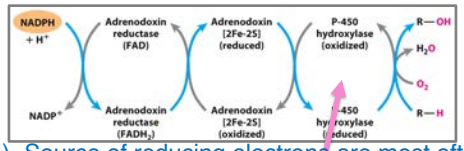
- The enzyme is a cytochrome called P-450
- The co-substrate electrons are from NADPH
- There is Cytochrome P-450 reductase to funnel electrons from co-substrate (B)

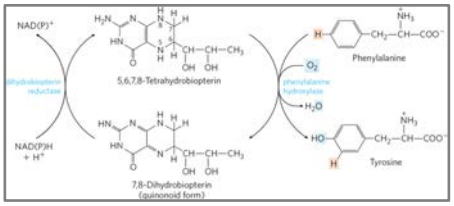
*a.k.a.: hydroxylase, mixed-function oxygenase, "mixed-function oxidase"

Amino Acid Degradation: Oxidases

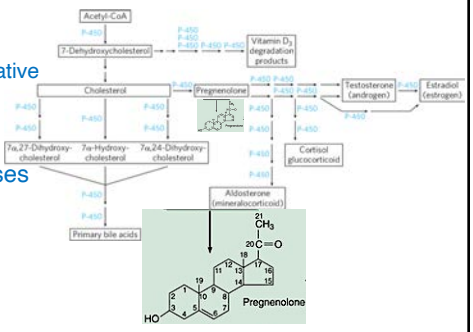
$RH + BH_2 + O_2 \rightarrow ROH + B + H_2O$ **Hydroxylases**

Example of P-450 reactions in adrenal gland:





1) Source of reducing electrons are most often NADPH (the co-substrate)
2) Other co-substrates
   a) FAD, FeS clusters, α-ketoglutarate (oxidative decarboxylation to succinate)
   b) Others: tetrahydrobiopterin (Phe hydroxylase)
3) Major class are the P-450 heme hydroxlases
   a) Expressed in liver and adrenal glands
   b) Steroids & fatty acids
   c) Xenobiotics (drugs)
      i. Specific
      ii. Non-specific
      iii. Inducible
      iv. Drug-drug interactions



Amino Acid Degradation: Oxidases

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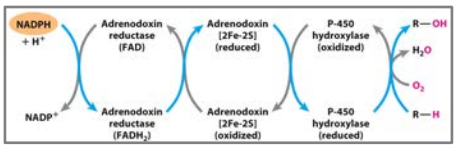
P-450 (CYP) reaction:



Major class of mono-oxygenases are the P-450-heme hydroxlases (>50 in humans)
a) Expressed in liver and adrenal glands
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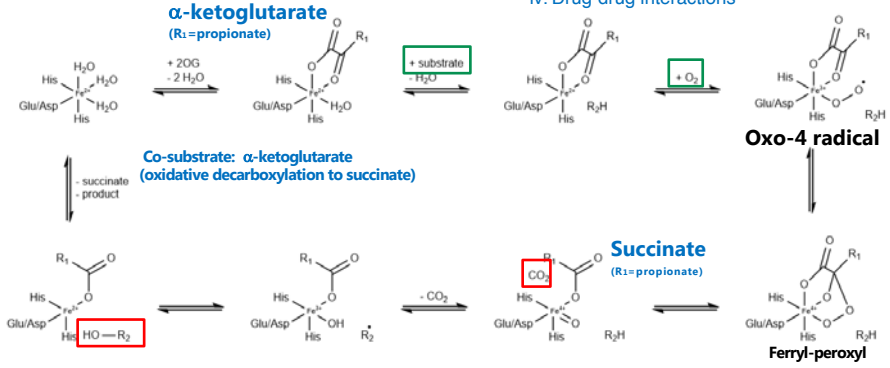

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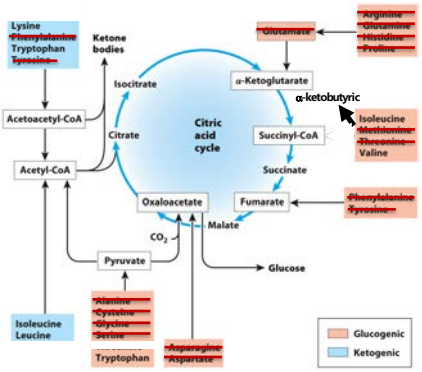

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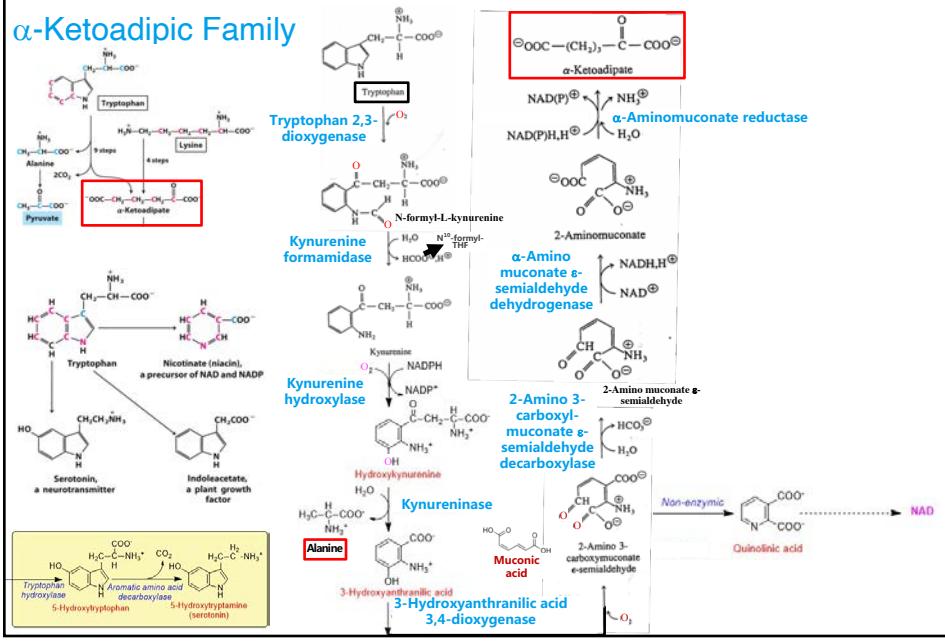
Before KW

Amino Acid Degradation

K,W

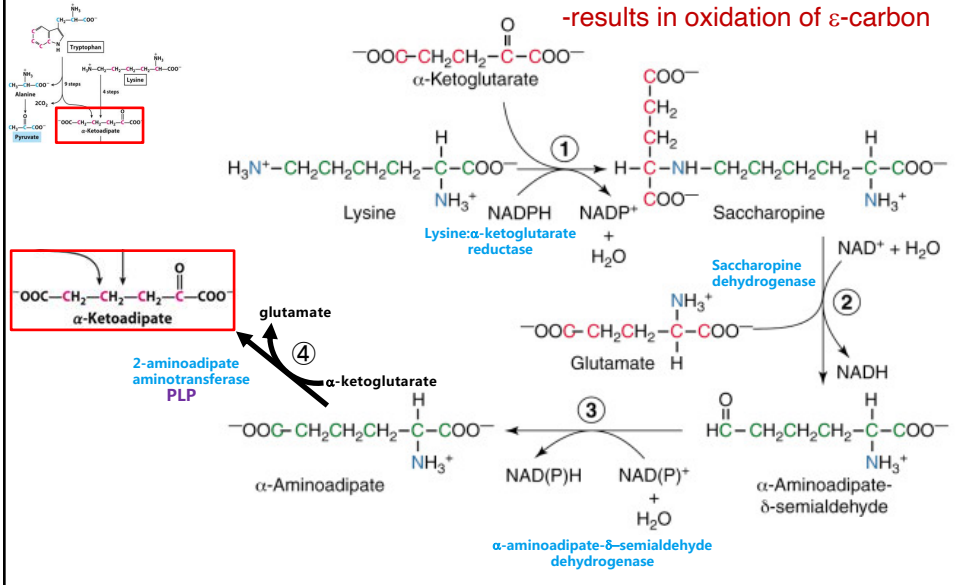
α-Ketoadipic Family



Amino Acid Degradation

α-Ketoadipic Family

-removal of ε-amino by reductive de-amination;
-results in oxidation of ε-carbon



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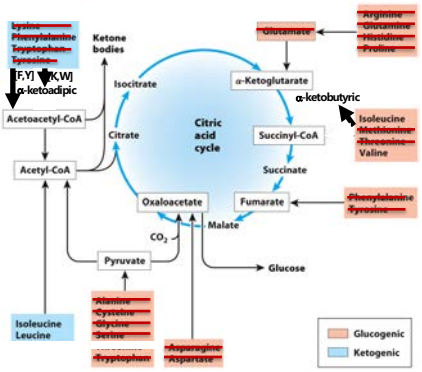

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Before VIL