Lehninger

SIXTH EDITION

Principles of Biochemistry

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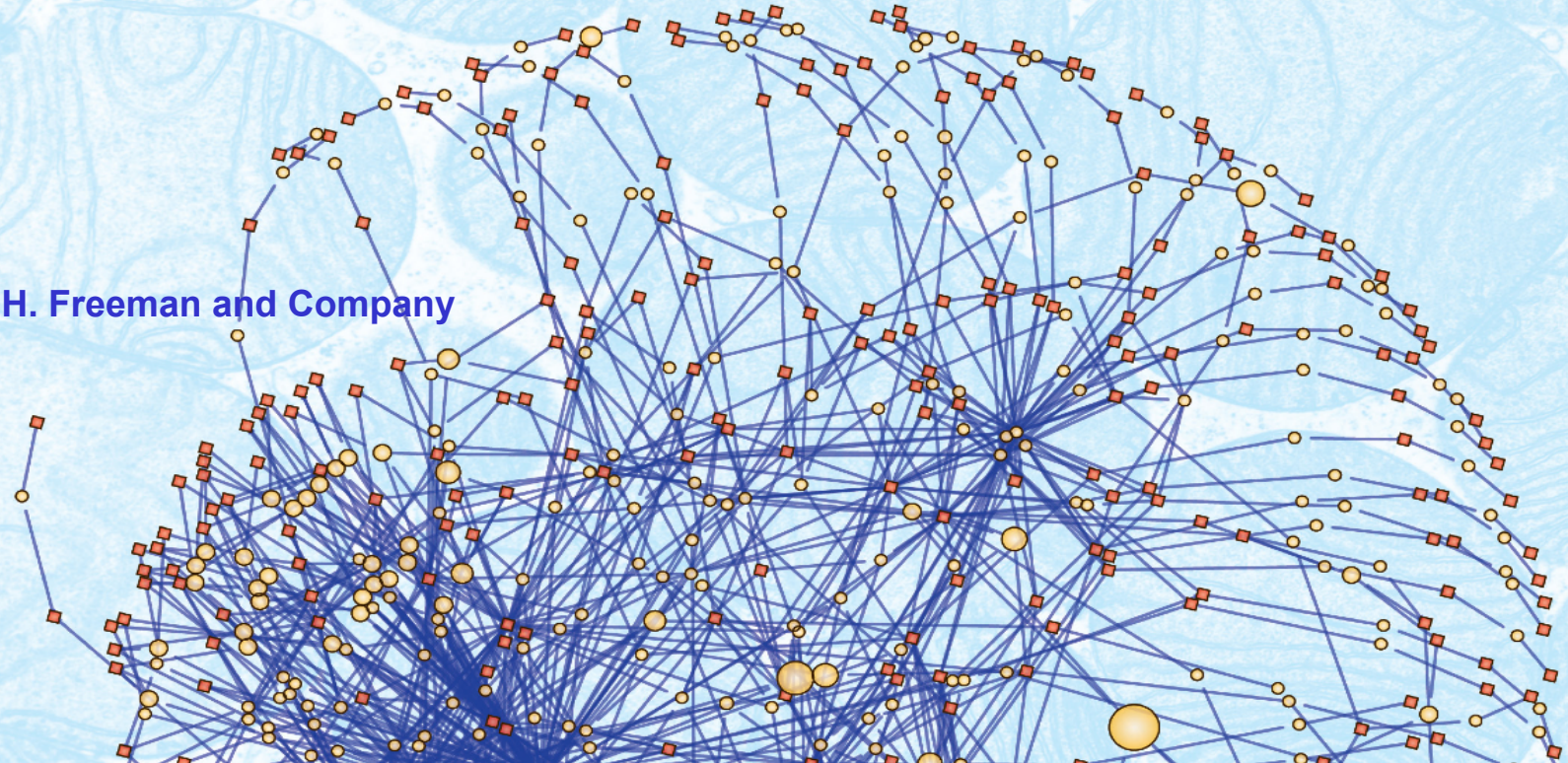
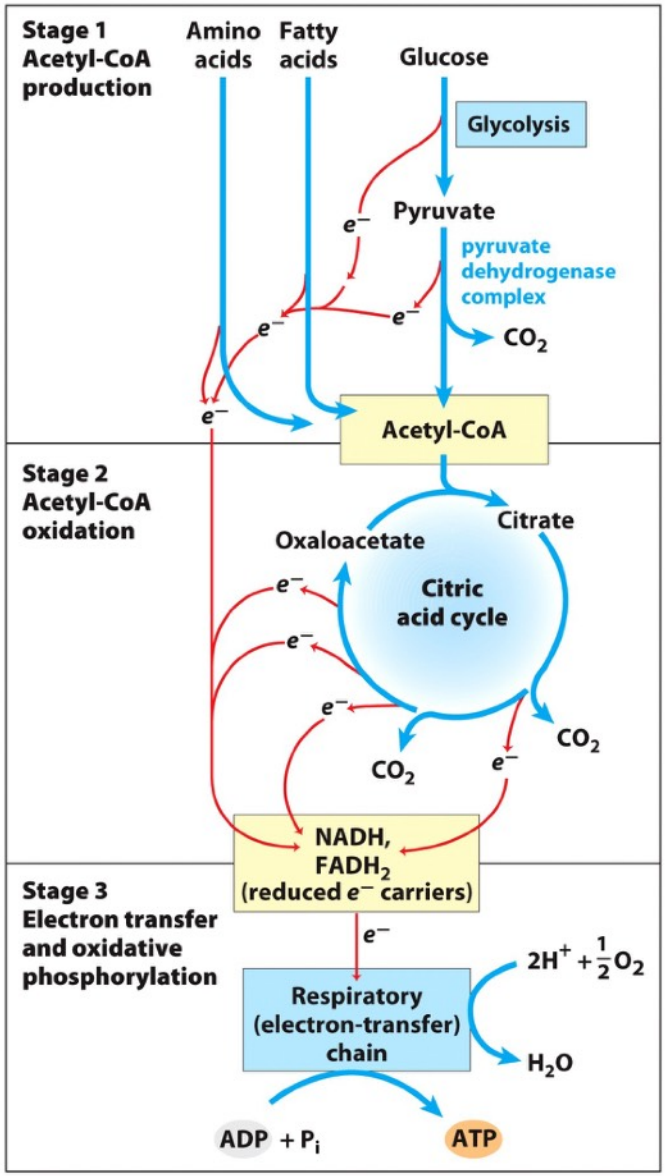
18| Amino Acid Oxidation and Production of Urea



Last Class of Biomolecules For Energy

1. Production of acetyl-CoA
   - Glucose
     - To pyruvate via glycolysis
     - To acetyl-CoA by PDH
   - Fatty acid
     - To acetyl-CoA via β oxidation
   - Amino acid
     - To acetyl-CoA via oxidation
2. Oxidation of acetyl-CoA via citric acid cycle
   - Generation of NADH and $FADH_2$
3. ATP production from NADH and $FADH_2$ via respiratory chain



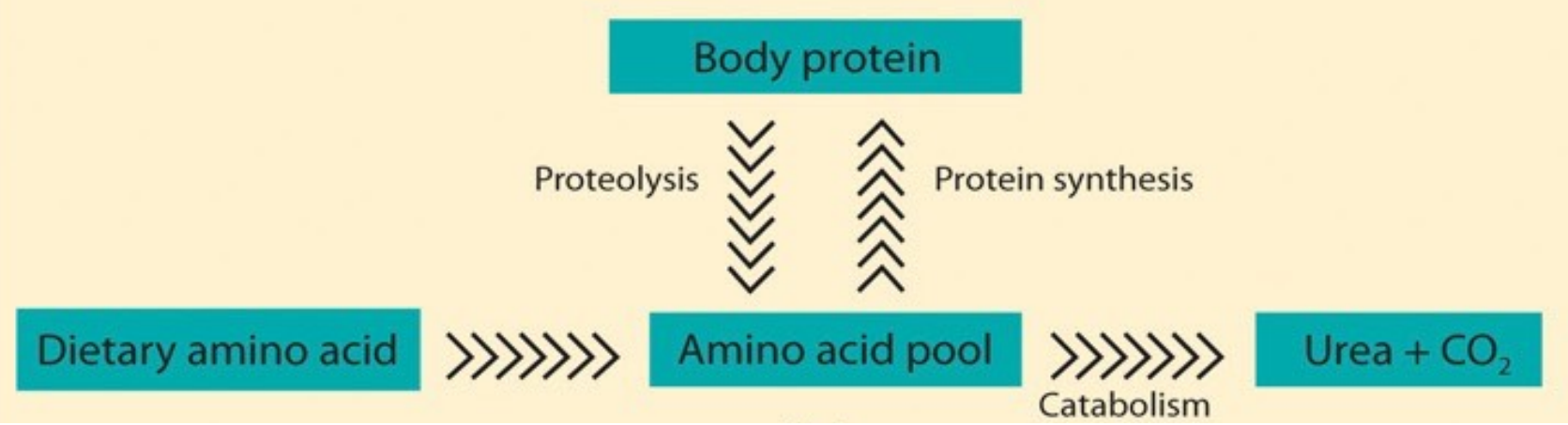
Use of Amino Acids As Fuel

- Carnivores. About 90% of energy needs can be met by amino acids immediately after a meal
- Herbivores. Only a small fraction of energy needs are met by oxidation of amino acids
- Plants do not use amino acids as a fuel source
  - Use carbohydrates produced in photosynthesis as sole energy source
  - Degrade amino acids to provide precursors for other biosynthetic pathways



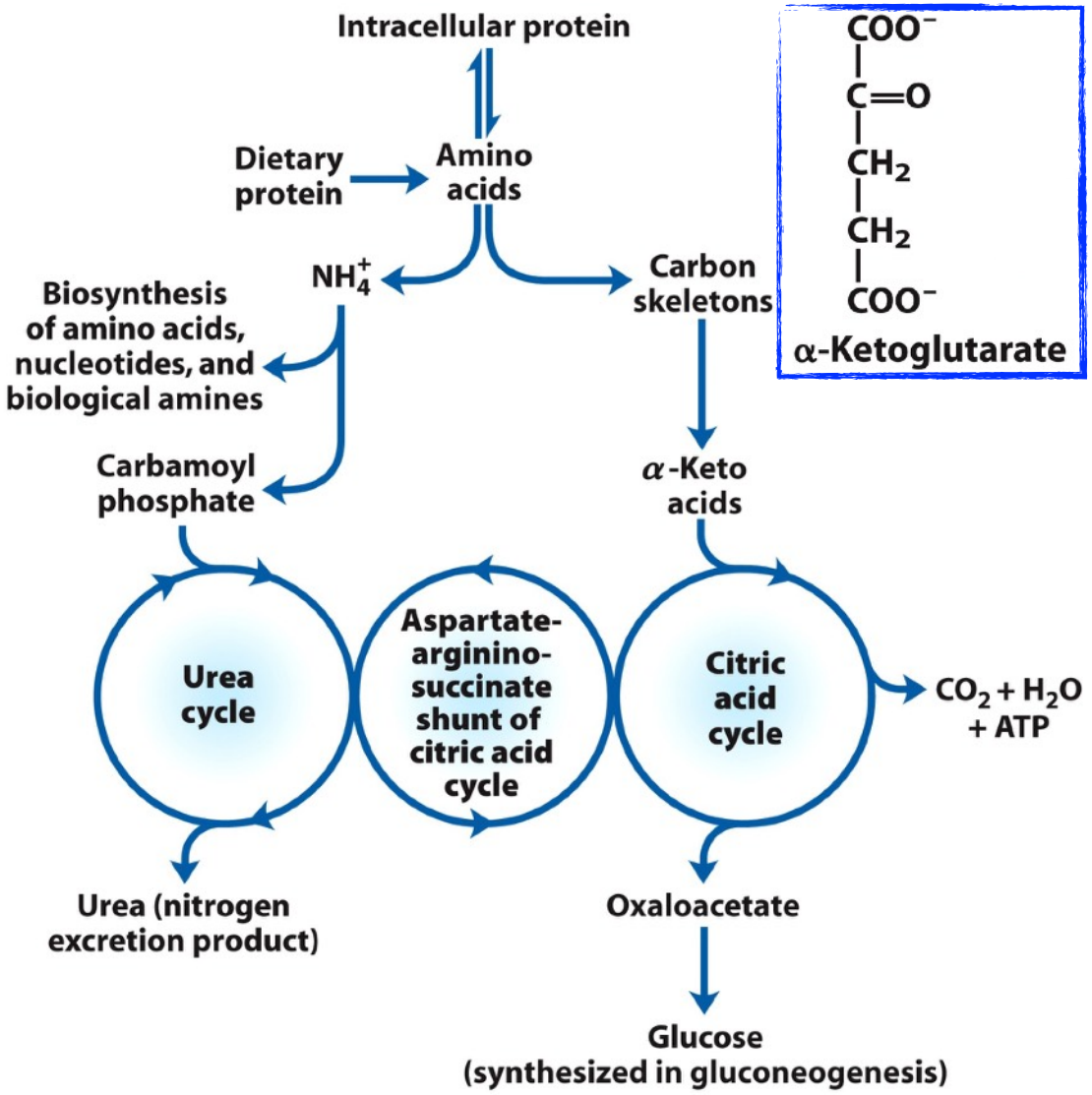
When to Degrade Amino Acids?

- During normal protein degradation and synthesis.
  - **Some** amino acids released from protein breakdown are not needed.
- When a diet is rich in protein.
  - Dietary amino acids **exceed** body's need for protein synthesis.
- During starvation.
  - Carbohydrates unavailable and amino acids used for **energy**.



Overview of Amino Acid Catabolism

- Feature of amino acids.
  - All contain amino groups.
- A key step.
  - Lose amino group.
  - Form α-keto acid.
- Amino group.
  - Reused or excreted.
- α-keto acid.
  - Oxidized or recycled.



Week 12 Chapter 18 Amino Acid Oxidation

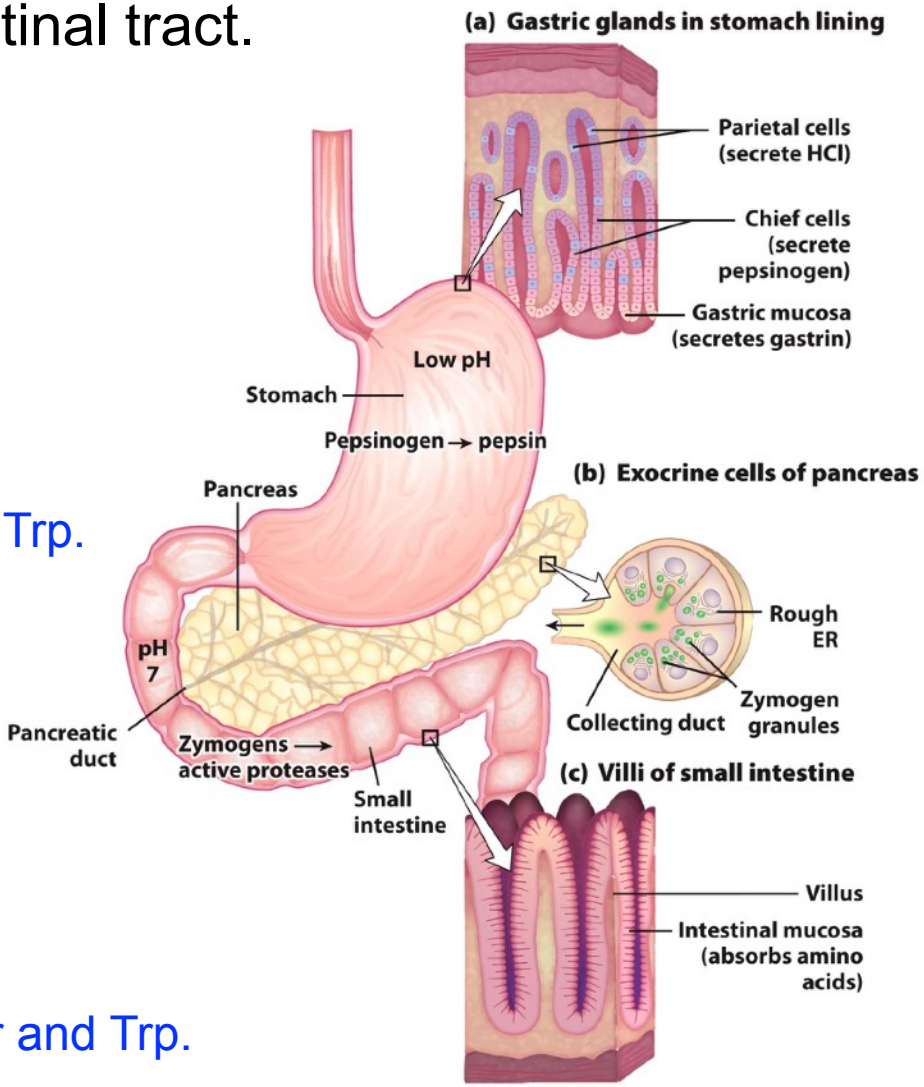
18.1 Metabolic Fates of Amino Groups

18.2 Nitrogen Excretion and Urea Cycle

18.3 Pathways of Amino Acid Degradation

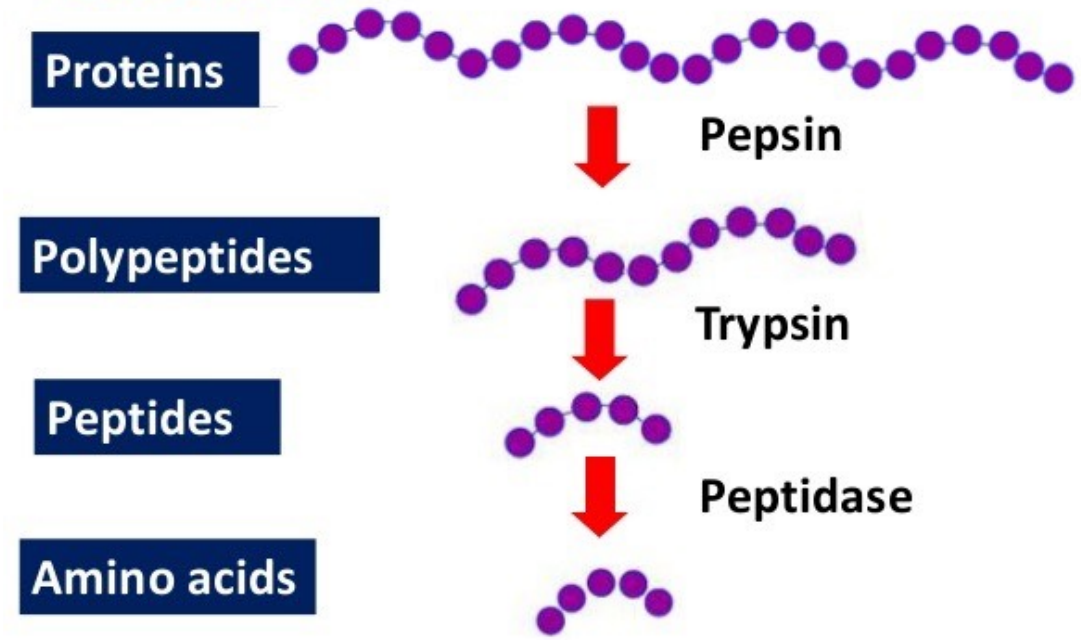
Protein Hydrolysis in Digestive Tract

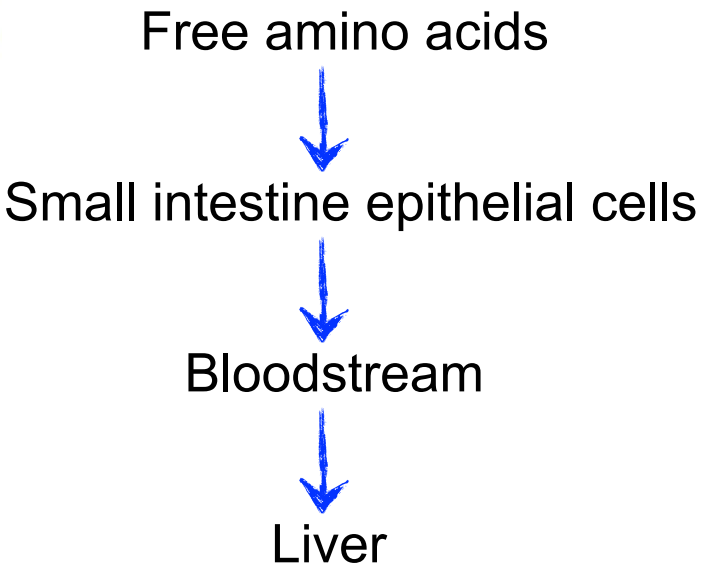
- Degradation occurs in gastrointestinal tract.
- In stomach.
  - Secretion of HCl (pH 1.0 - 2.5).
    - Antiseptic.
    - Denaturing.
  - Secretion of pepsinogen.
    - Conversion to active pepsin.
    - Pepsin cleaves before Phe, Tyr and Trp.
- In small intestine.
  - Secretion of bicarbonate (pH 7).
  - Secretion of trypsinogen and chymotrypsinogen.
    - Conversion to active proteases.
    - Trypsin cleaves after Lys and Arg.
    - Chymotrypsin cleaves after Phe, Tyr and Trp.



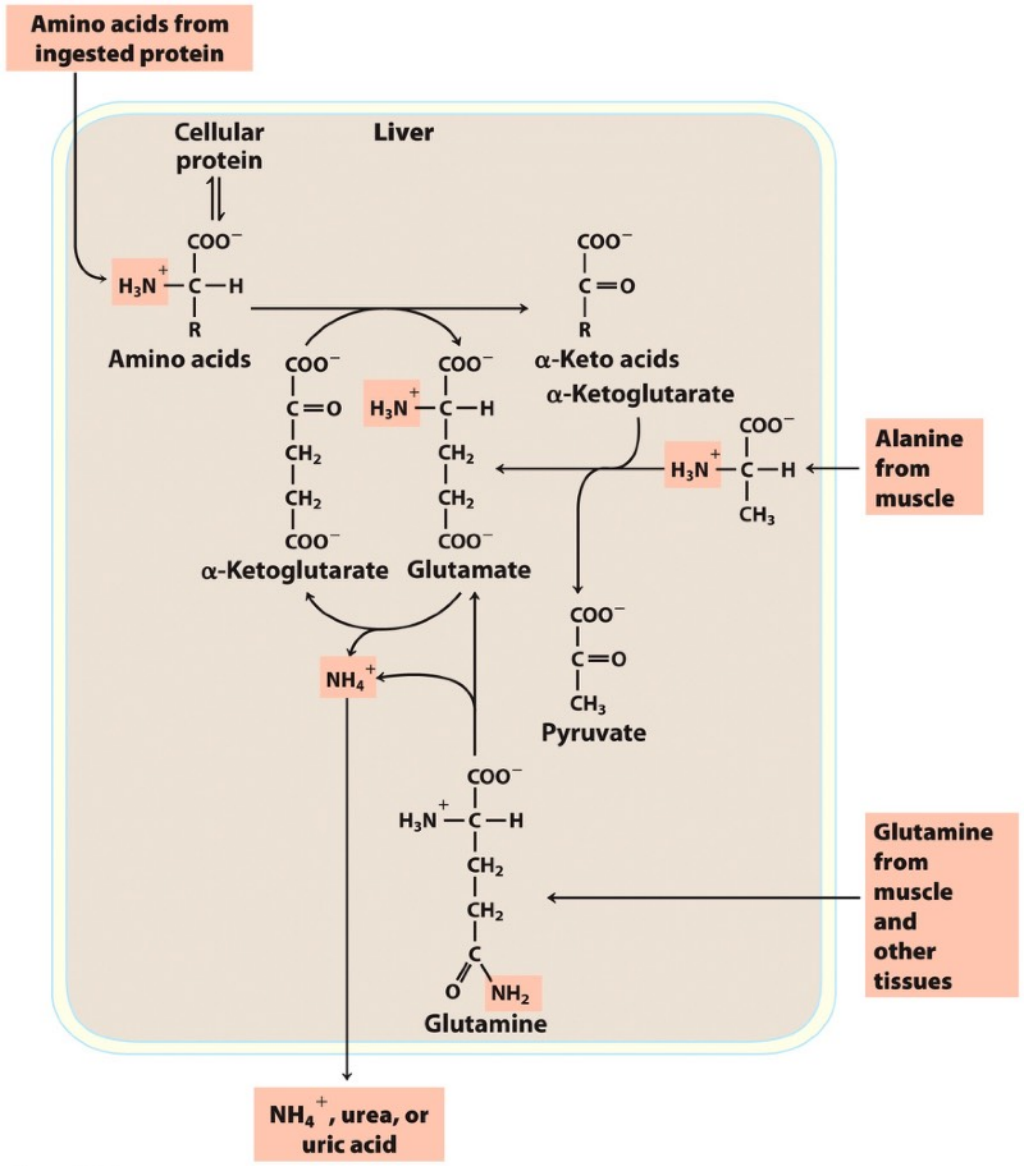
Dietary Proteins Are Hydrolyzed

- Pepsin cuts protein into peptides in the stomach.
- Trypsin and chymotrypsin cut proteins and larger peptides into smaller peptides in the small intestine.
- Aminopeptidase and carboxypeptidase degrade peptides into amino acids in the small intestine.



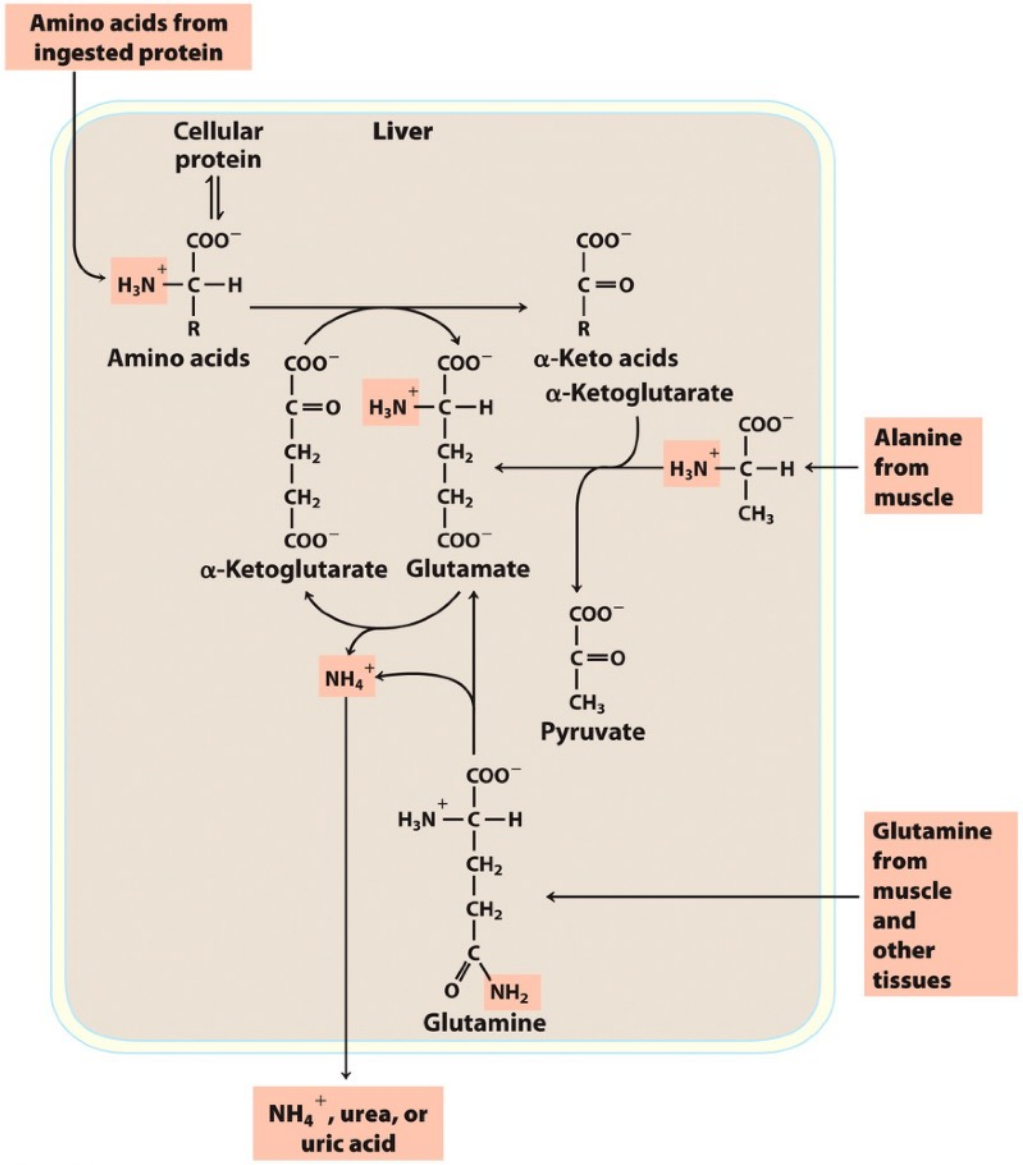


Amino Group Catabolism



- Most amino acids are metabolized in liver.
- Amino group is removed as ammonia.
  - Some ammonia is recycled and used in biosynthesis.
  - Excess ammonia is excreted.
- Ammonia generated in other (extrahepatic) tissues are transported to liver.

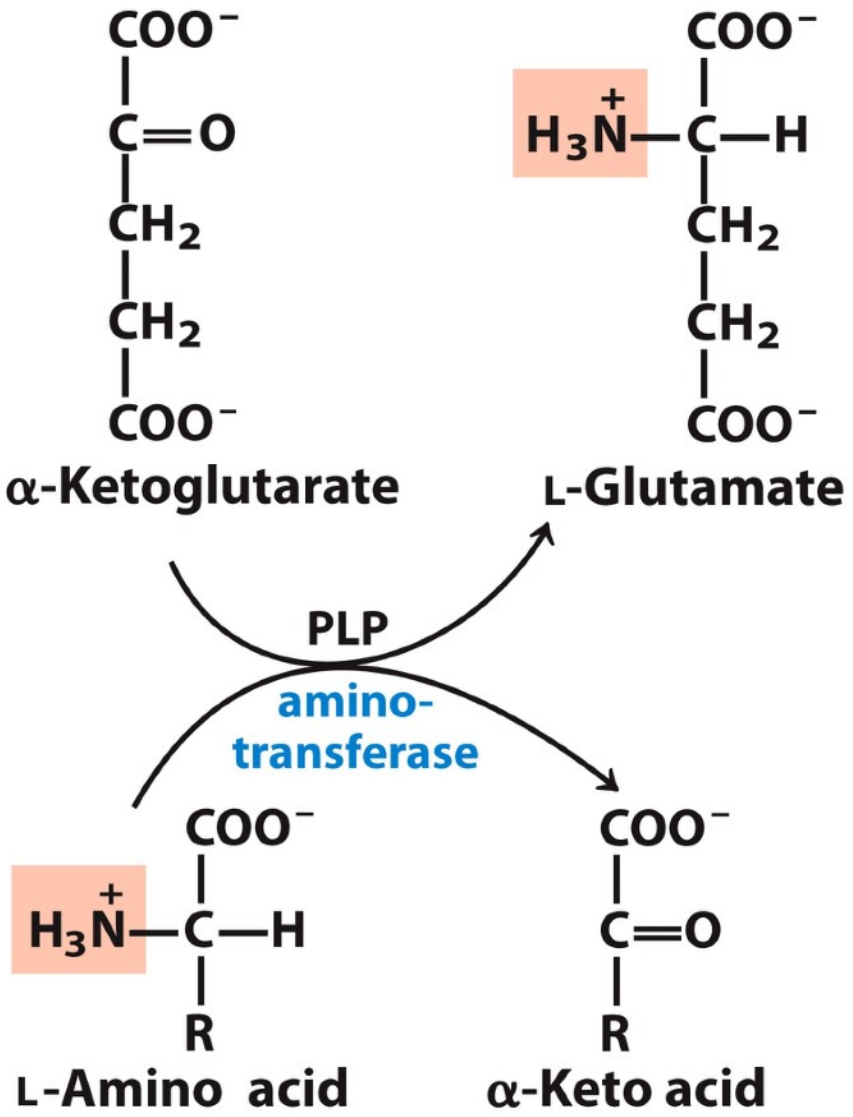
Four Amino Acids in Nitrogen Catabolism



- Glutamate and Glutamine.
  - Collect amino groups.
  - Glutamine transports ammonia from extrahepatic tissues to liver.
  - Convert to α-ketoglutarate.
- Alanine.
  - Transports ammonia from skeletal muscles to liver.
- Aspartate.
  - Donates amino group for urea production.

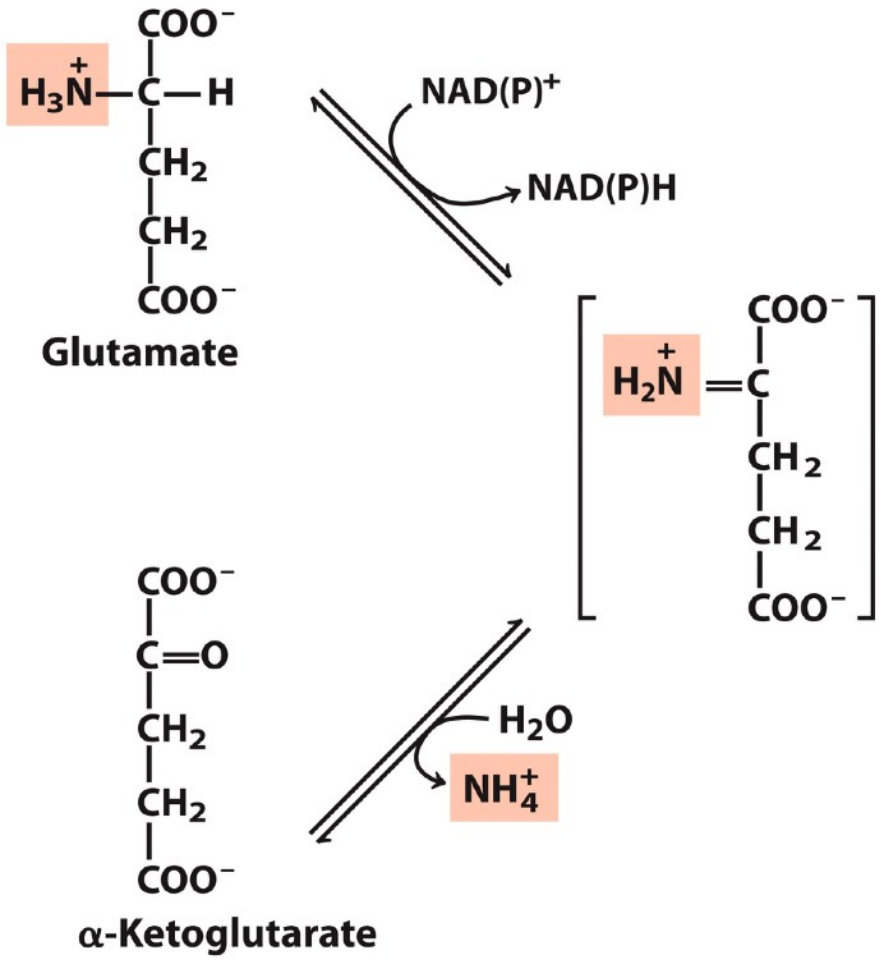
Enzymatic Transamination

- First step in amino acid catabolism in liver.
  - Removal of α-amino group.
  - Catalyzed by aminotransferase or transaminase (reversible).
- α-ketoglutarate is a general acceptor of amino group.
  - Reactants: amino acid and α-ketoglutarate.
- Glutamate is a temporary storage of amino group.
  - Products: α−keto analog of amino acid and glutamate.



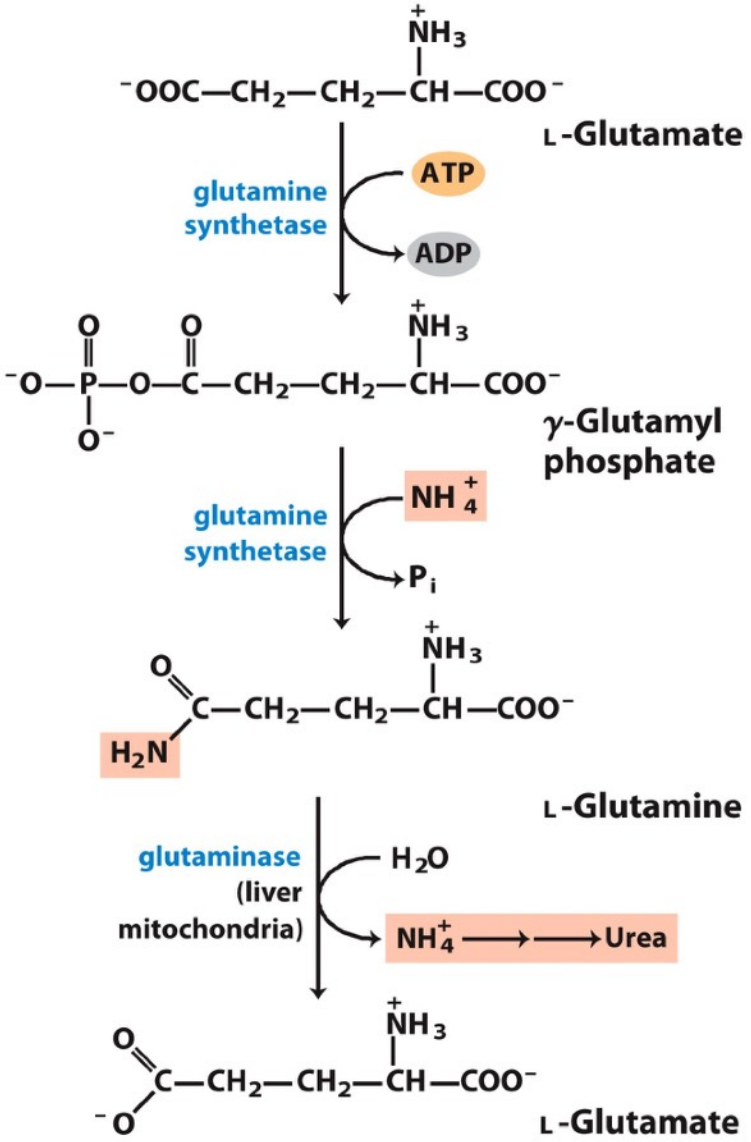
Glutamate Releases Amino Group

- Oxidative deamination occurs in mitochondria.
  - Glutamate transported from cytosol to mitochondria in hepatocyte.
  - Catalyzed by glutamate dehydrogenase.
  - $NAD(P)^+$ is reduced to NAD(P)H.
- Products: α-ketoglutarate and ammonia.
  - Ammonia processed to urea for excretion.
- Transdeamination = transamination + oxidative deamination.



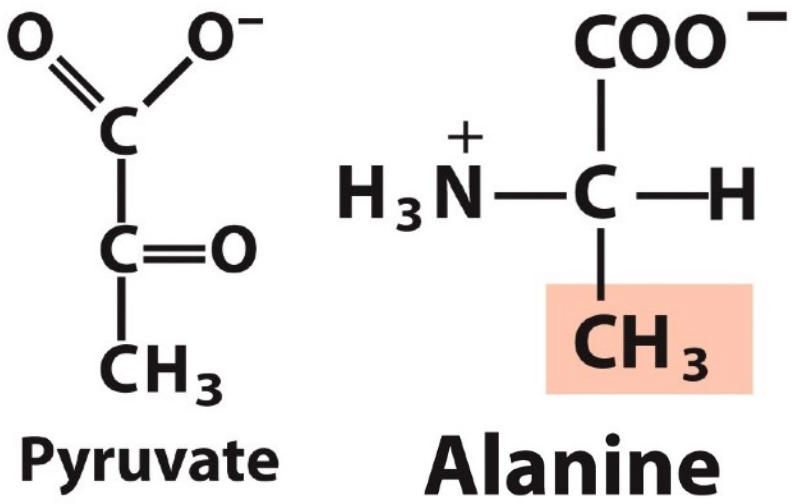
Glutamine Transports Ammonia

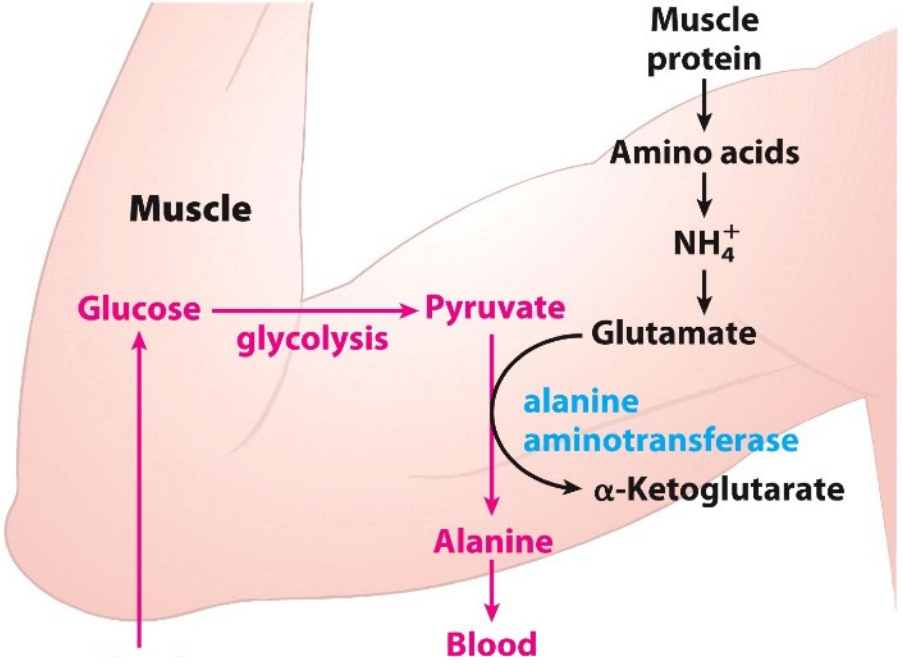
- Free ammonia is very toxic.
  - Needs to be converted to a nontoxic compound.
  - Cannot be transported directly in blood.
- Glutamine is a nontoxic transport form of ammonia.
  - Transported from extrahepatic tissues to liver in bloodstream.
  - Present in much higher concentration than other amino acids.
- Glutamine is transported to liver.
  - Releases ammonia and glutamate.



Alanine Transports Ammonia From Muscle

- Alanine plays a special role in transporting ammonia.
  - Glutamate can be converted to glutamine for transport.
  - Glutamate can also donate amino group to pyruvate, and form alanine for transport.



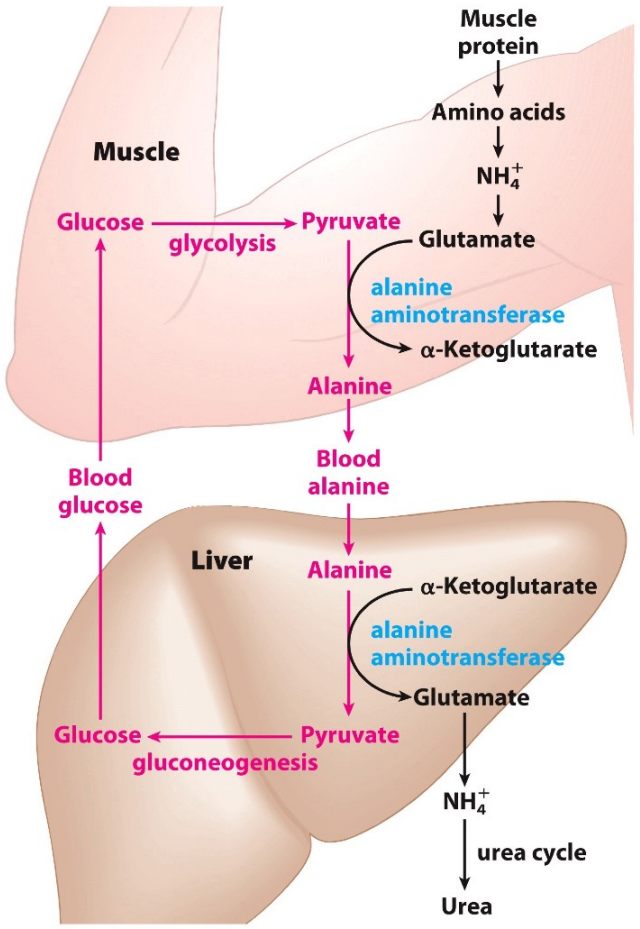


Four Enzyme-Catalyzed Reactions

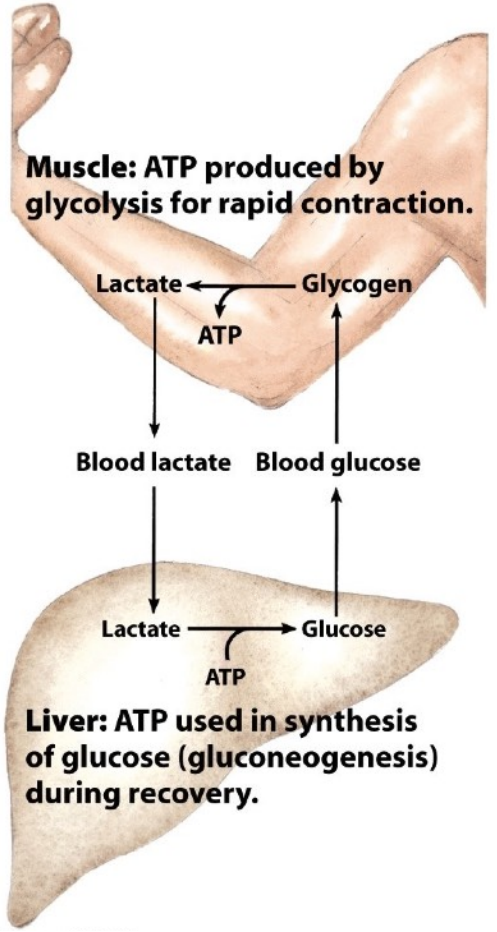
- Amino acid + α-ketoglutarate -> α-keto acid + glutamate.
  - **Transamination** reaction catalyzed by aminotransferase.
  - Glutamate is a general collection point of amino groups.
  - Special case: pyruvate + glutamate -> alanine + α-ketoglutarate.
- Glutamate -> ammonia + α-ketoglutarate.
  - Oxidative **deamination** reaction catalyzed by glutamate dehydrogenase.
  - $NAD(P)^+$ is reduced to NAD(P)H.
  - Separation of amino group and carbon skeleton.
- Glutamate + ammonia -> glutamine.
  - Condensation reaction catalyzed by glutamine synthetase.
  - ATP is consumed and form ADP.
  - **Production of glutamine** as ammonia carrier to transport in bloodstream.
- Glutamine -> glutamate + ammonia.
  - Hydrolysis reaction catalyzed by glutaminase.
  - **Ammonia is released** from glutamine.

Glucose-Alanine Cycle vs. Cori Cycle

- Vigorously working muscles.
  - Anaerobic condition.
  - Rely on glycolysis for energy.
  - Glucose -> Pyruvate.
- Pyruvate -> alanine.
  - Transport in blood.
  - Alanine -> glucose in liver.
- Pyruvate -> lactate.
  - Transport in blood.
  - Lactate -> glucose in liver.



Glucose-Alanine Cycle



Cori Cycle

Summary 18.1 Metabolic Fates of NH_2

- Human normally derive a small fraction of oxidative energy from amino acid catabolism. Ingested proteins are degraded by proteases in stomach and small intestine.
- The first step in amino acid catabolism is separation of amino group from carbon skeleton. Amino group is transferred to α-ketoglutarate to form glutamate.
- Glutamate is transported from cytosol to mitochondria, and converted to α-ketoglutarate and ammonia. Ammonia formed in extrahepatic tissues is transported to liver as glutamine or alanine.

Week 12 Chapter 18 Amino Acid Oxidation

18.1 Metabolic Fates of Amino Groups

18.2 Nitrogen Excretion and Urea Cycle

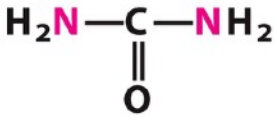
18.3 Pathways of Amino Acid Degradation

Fates of Nitrogen in Organisms

- Fish release amino nitrogen as ammonia (ammonotelic).
  - Toxic ammonia is diluted in water.
- Humans excrete amino nitrogen as urea (ureotelic).
  - Urea is far less toxic than ammonia.
  - Urea has very high solubility in water (urine).
- Birds and reptiles excrete amino nitrogen as uric acid (uricotelic).
  - Uric acid is rather insoluble in water.
  - Excretion as paste allows the animals to conserve water.
- Plants conserve almost all amino groups.

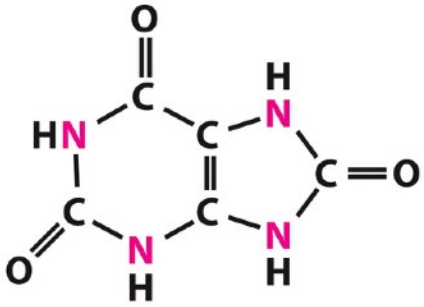
Ammonia (as ammonium ion)

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia



Urea

Ureotelic animals: many terrestrial vertebrates; also sharks



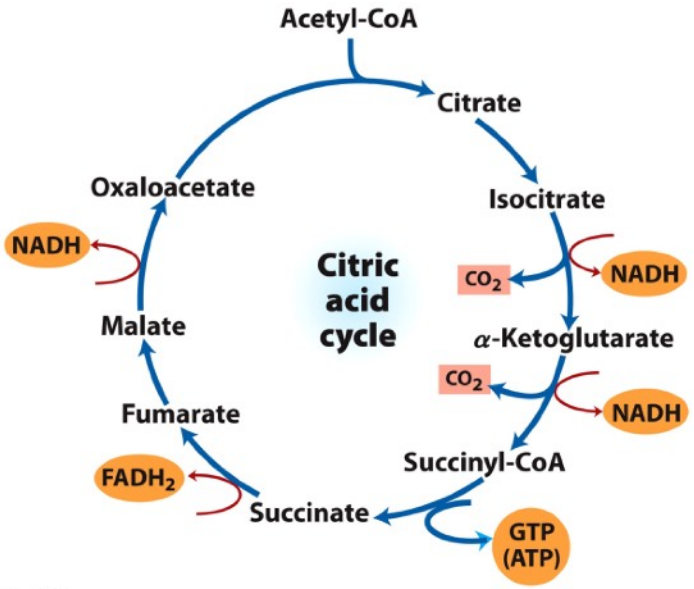
Uric acid

Uricotelic animals: birds, reptiles

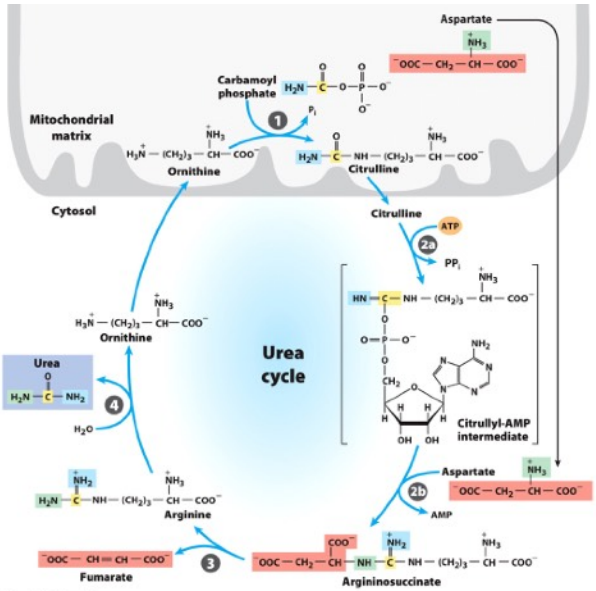
Ammonia is Converted to Urea in Human

- Ammonia deposited in hepatocyte mitochondria is converted to urea in urea cycle.
  - Pathway discovered by Hans Krebs, who later discovered citric acid cycle.
  - Occurs in liver.
  - Urea passes into bloodstream, to kidney, and excreted in urine.

Hans Krebs, 1900–1981



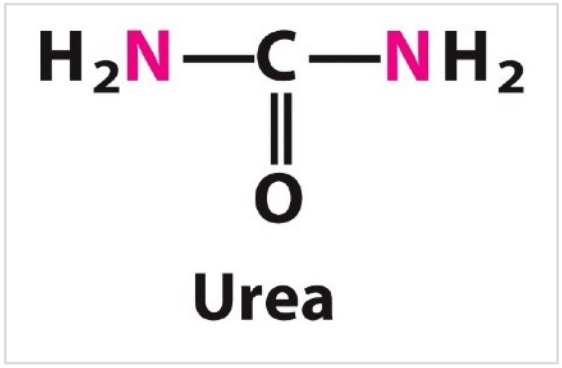
Citric Acid Cycle

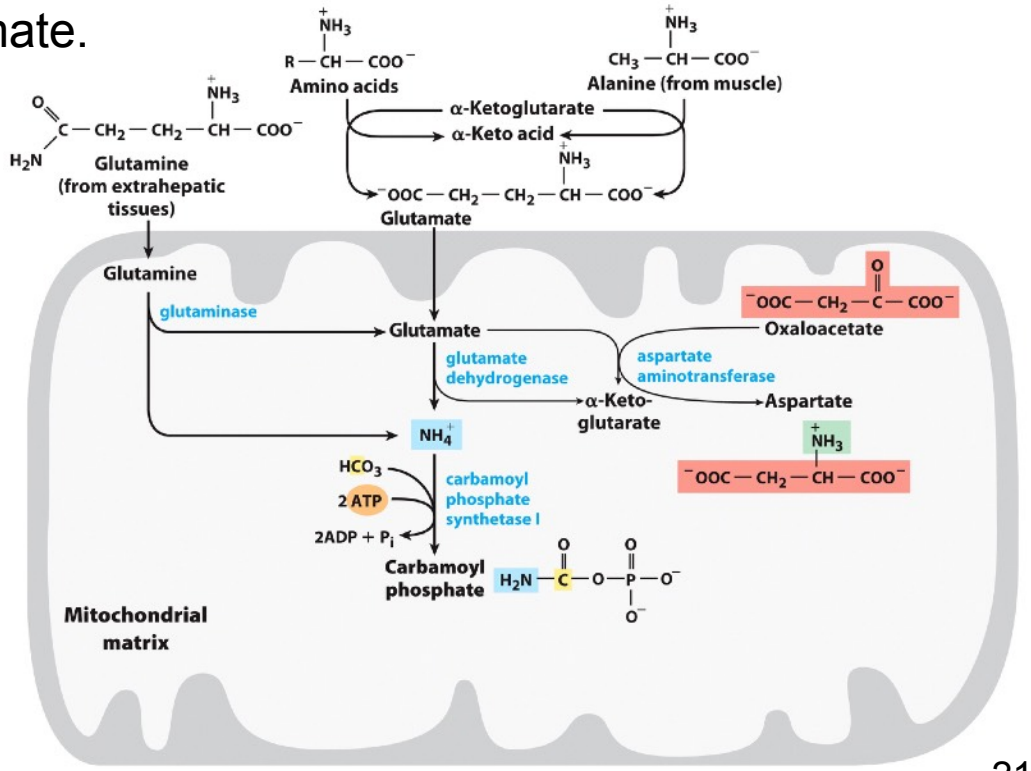


Urea Cycle

Excess Glutamate is Metabolized

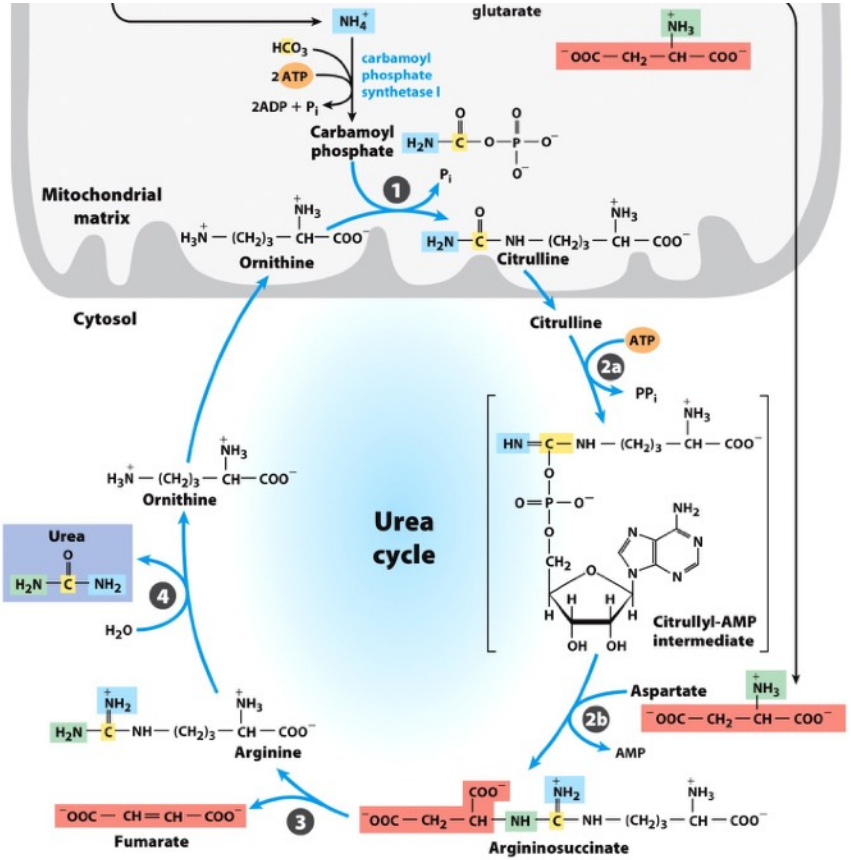
- Glutamate is metabolized in hepatocyte mitochondria.
  - Source of glutamate:
    - Transamination of α-ketoglutarate by amino acids including alanine.
    - Deamination of glutamine.
  - Source of ammonia.
    - Oxidative deamination of glutamate.
    - Deamination of glutamine.
  - Fate of ammonia.
    - Urea.





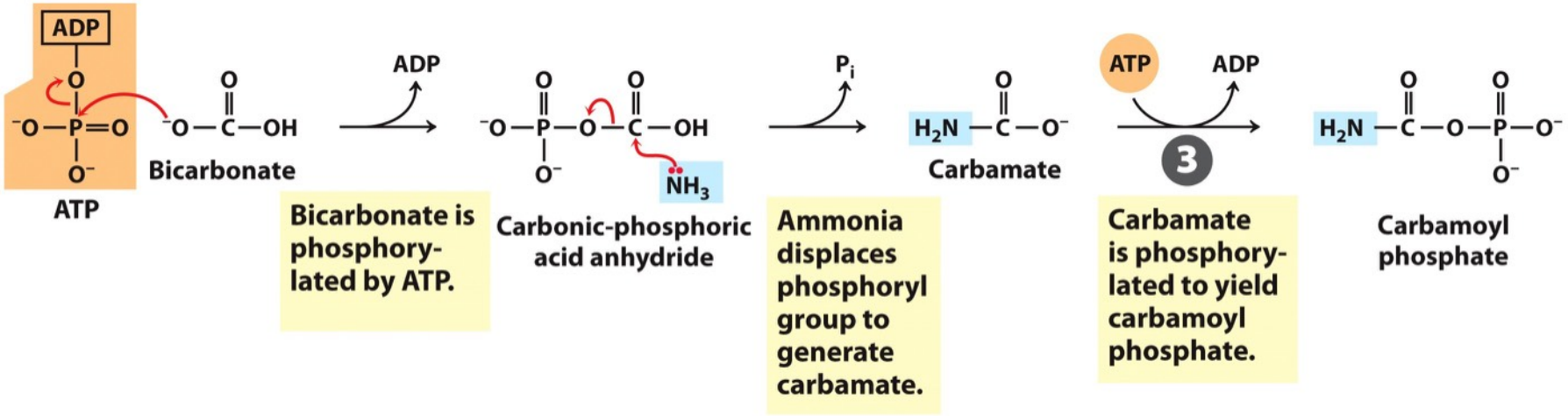
Ammonia -> Urea in Five Steps

- First 2 reactions in mitochondria
  1. Ammonia + bicarbonate -> carbamoyl phosphate.
  2. Carbamoyl phosphate + ornithine -> citrulline.
- Last 3 reactions in cytosol
  3. Citrulline + aspartate -> argininosuccinate.
  4. Argininosuccinate -> arginine + fumarate.
  5. Arginine -> urea + ornithine.
- Overall equation.
  - $NH_4^+ + HCO_3^- +$ aspartate + 3 ATP -> urea + fumarate + 2 ADP + AMP



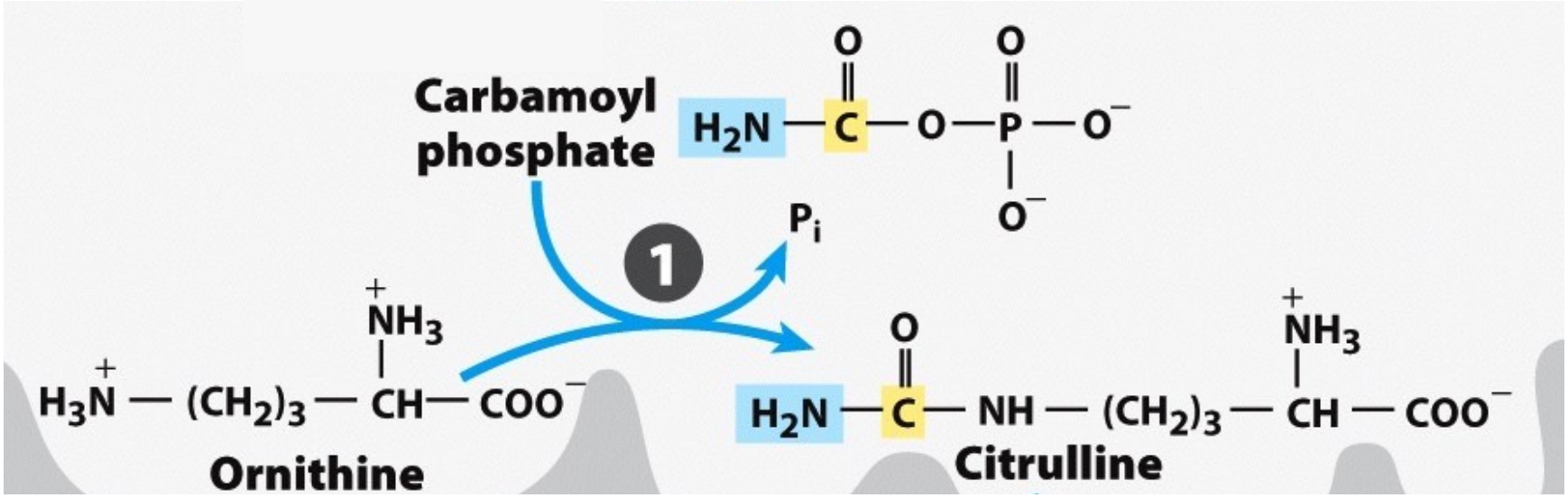
Step 1. Ammonia -> Carbamoyl Phosphate

- Ammonia + bicarbonate -> carbamoyl phosphate.
  - Consumes two molecules of ATPs (two activation steps).
    - Bicarbonate is activated by phosphorylation by ATP, forming an anhydride.
    - Ammonia attacks carbonyl carbon atom, forming a carbamate.
    - Carbamate is activated by phosphorylation by ATP, forming an anhydride.
  - Catalyzed by carbamoyl synthetase I.
  - First nitrogen-acquiring reaction in urea synthesis (from ammonia).



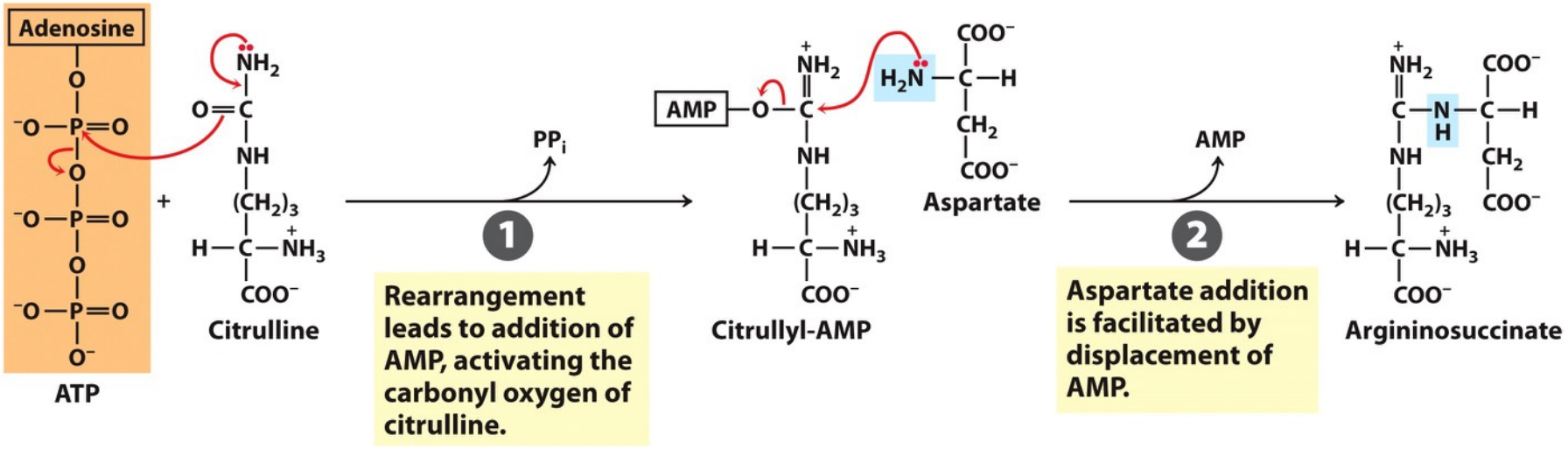
Step 2. Ornithine -> Citrulline

- Carbamoyl phosphate + ornithine -> citrulline
  - Carbamoyl phosphate enters urea cycle as an activated carbamoyl group donor
  - Ornithine accepts carbamoyl group to form citrulline, with release of P_i
    - Ornithine NOT one of 20 common amino acids
    - Similar to oxaloacetate in citric acid cycle (accept entry molecule and is regenerated)
  - Catalyzed by ornithine transcarbamoylase



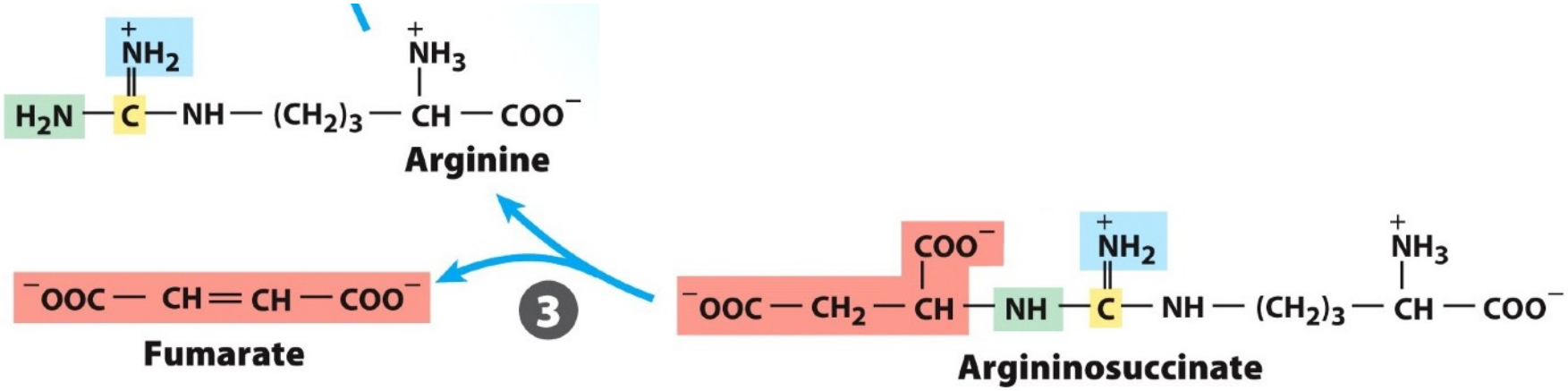
Step 3. Citrulline -> Argininosuccinate

- Citrulline + aspartate -> argininosuccinate.
  - Citrulline travels from mitochondria to cytosol.
  - Consumes two equivalents of ATPs (ATP -> AMP).
    - Citrulline is activated by attachment to AMP.
    - Aspartate amino group attacks citrulline carbon.
  - Catalyzed by argininosuccinate synthetase.
  - Second nitrogen-acquiring reaction in urea synthesis (from aspartate).



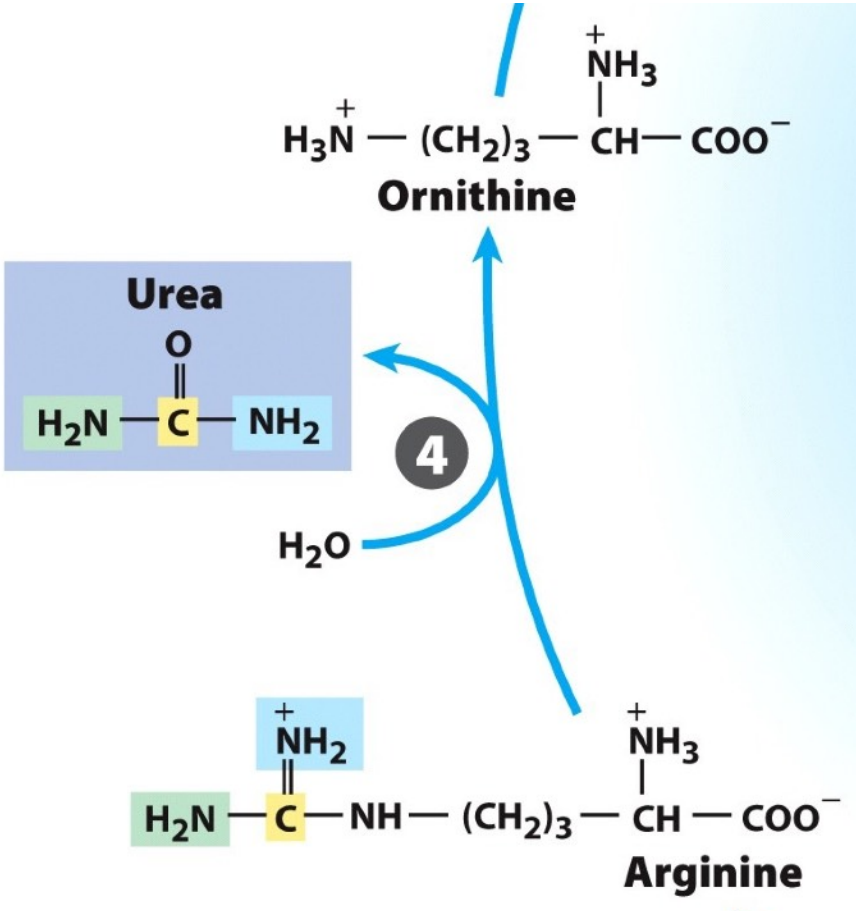
Step 4. Argininosuccinate -> Arginine

- Argininosuccinate -> fumarate + arginine.
  - Fumarate -> malate -> enter mitochondrial citric acid cycle.
  - Arginine contains nitrogen and carbon atoms that are released as urea.
    - 1 nitrogen atom from ammonia.
    - 1 nitrogen atom from aspartate.
    - 1 carbon atom from bicarbonate.
  - Catalyzed by argininosuccinase.
  - The only reversible reaction in urea cycle.



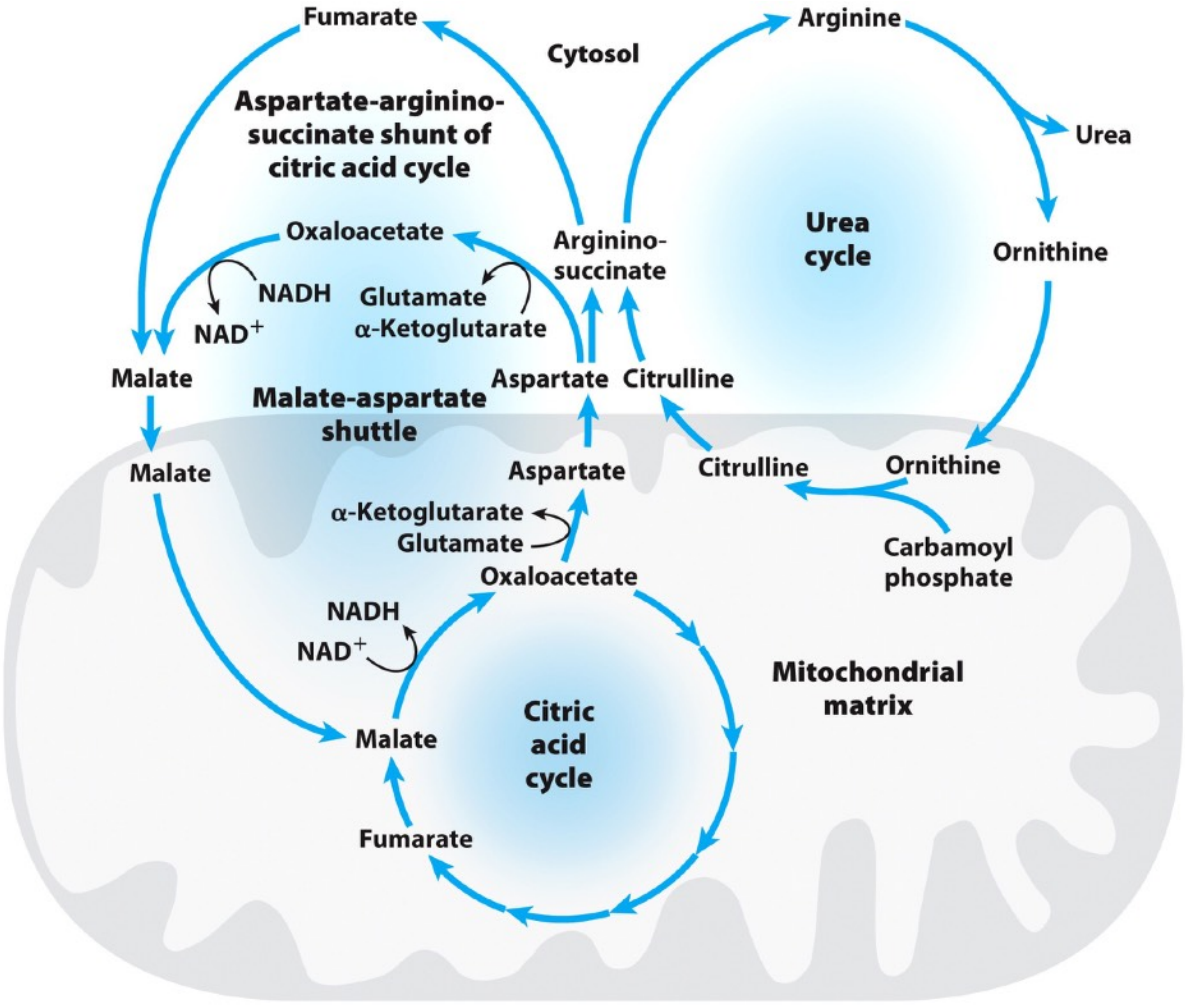
Step 5. Arginine -> Urea + Ornithine

- Arginine -> urea + ornithine.
  - Net production of urea.
    - 1 nitrogen atom from ammonia.
    - 1 nitrogen atom from aspartate.
    - 1 carbon atom from bicarbonate.
  - Ornithine travels from cytosol to mitochondria.
  - Catalyzed by arginase.

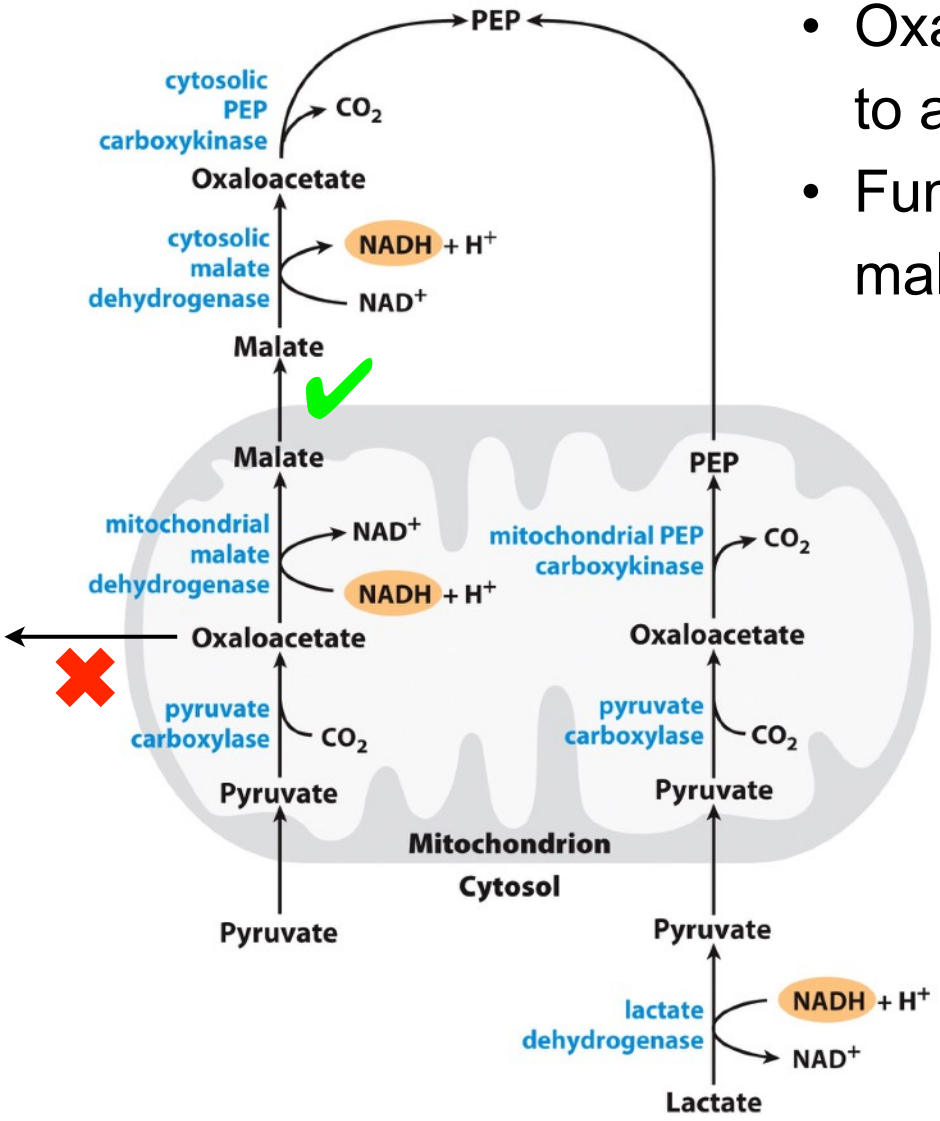


Urea Cycle and CAC Can Be Linked

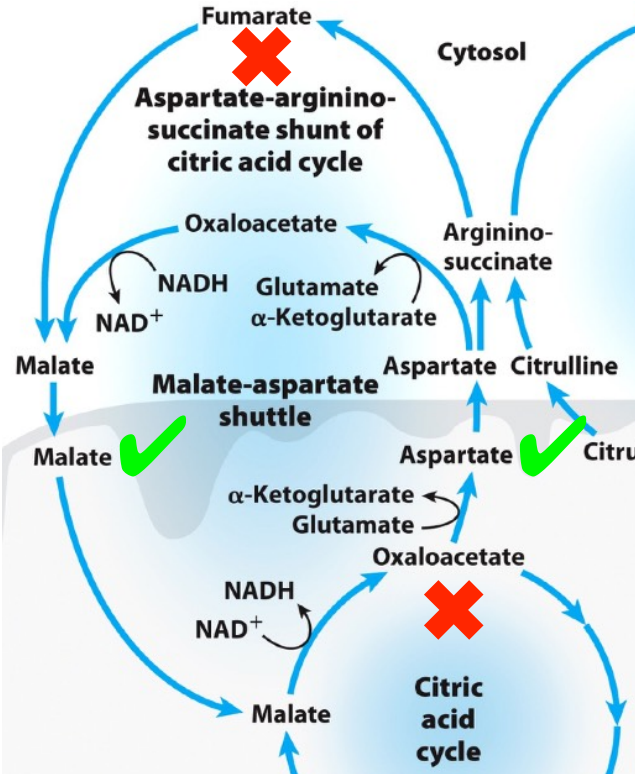
- Urea cycle produces fumarate in cytosol.
  - Fumarate -> malate.
  - Malate enters mitochondrial CAC.
- Citric acid cycle produces oxaloacetate in mitochondria.
  - Oxaloacetate -> aspartate.
  - Aspartate enters cytosol urea cycle.



No Transporter for Oxaloacetate/Fumarate

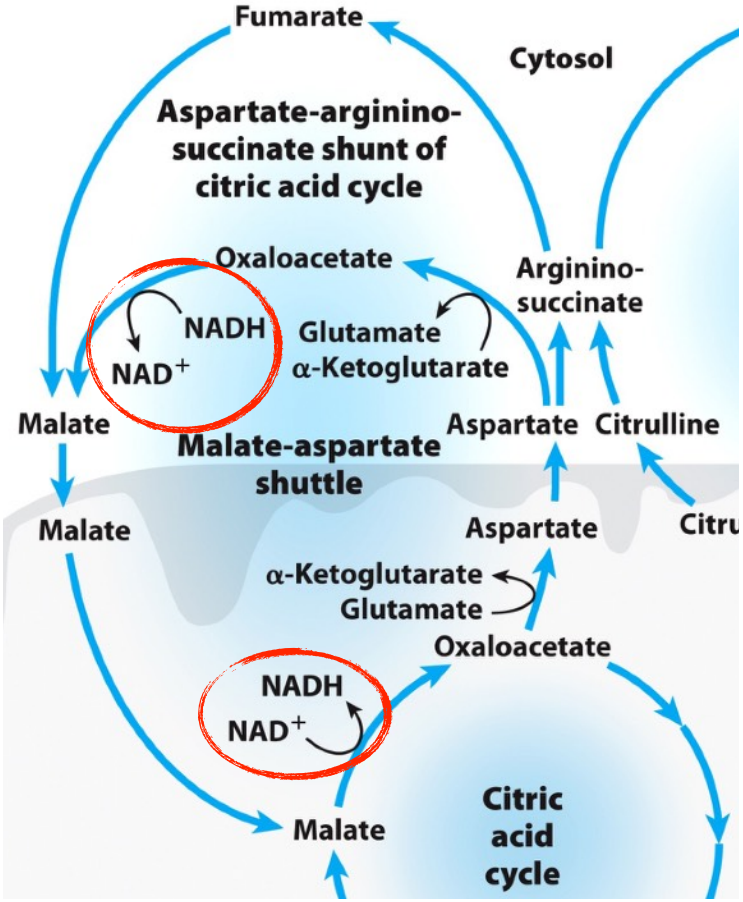


- Oxaloacetate needs to be converted to aspartate to exit mitochondria.
- Fumarate needs to be converted to malate to enter mitochondria.



NADH Shuttle Systems

- Mitochondrial membrane NOT permeable to NADH.
- How can NADH generated by glycolysis in cytosol be transported to respiratory chain in mitochondria?
  - In cytosol.
    - Aspartate -> oxaloacetate (transamination).
    - Oxaloacetate -> malate (reduction, with NADH oxidized to NAD^+).
    - Malate enters mitochondria.
  - In mitochondria.
    - Malate -> oxaloacetate (oxidation, with NAD^+ reduced to NADH).
    - Oxaloacetate -> aspartate (transamination).
    - Aspartate enters cytosol.



Net Result: Cytosolic NADH becomes mitochondrial NADH.

Summary 18.2 N Excretion + Urea Cycle

- Ammonia is highly toxic to human, and is excreted as urea in human.
- In urea cycle, ornithine combines with ammonia (in the form of carbamoyl phosphate) to form citrulline. A second amino group is transferred to citrulline from aspartate to form arginine. Arginase catalyzes hydrolysis of arginine to produce urea and ornithine.
- Urea cycle results in a net (carbon skeleton) conversion of oxaloacetate to fumarate, both of which are intermediates in citric acid cycle. These two cycles are thus interconnected, and referred to as “Krebs bicycle”.

Week 12 Chapter 18 Amino Acid Oxidation

18.1 Metabolic Fates of Amino Groups

18.2 Nitrogen Excretion and Urea Cycle

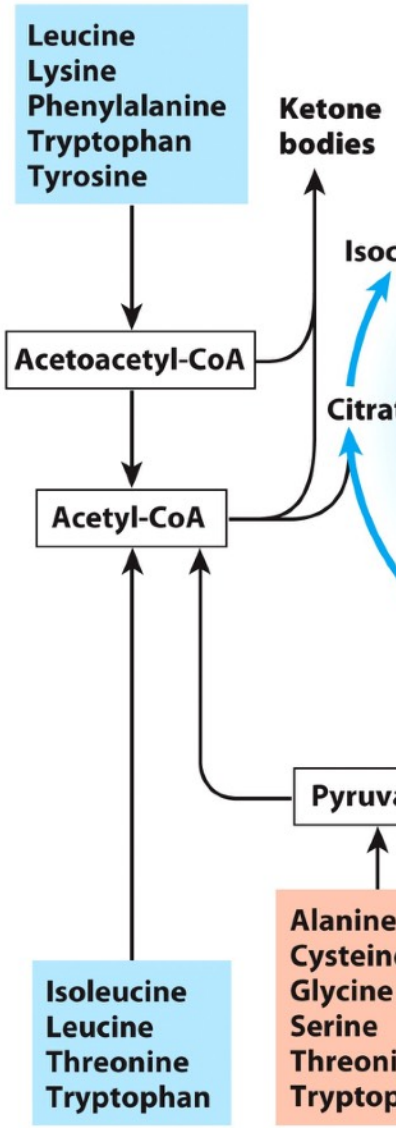
18.3 Pathways of Amino Acid Degradation

End Products of Amino Acid Degradation

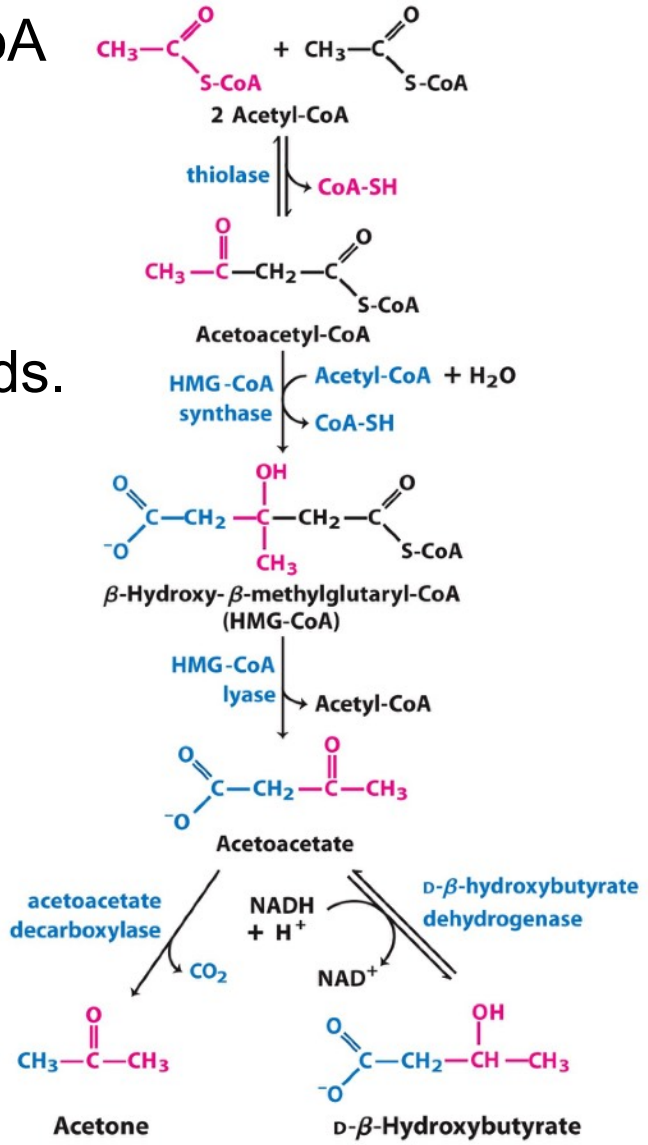
- 20 Catabolic pathways converge to form 6 major products, all of which enter citric acid cycle.
  - Ketogenic amino acids can be converted to ketone bodies.
  - Glucogenic amino acids can be converted to glucose.
- Some amino acids result in more than one product.

Seven to acetyl-CoA	Leu, Ile, Thr, Lys, Phe, Tyr, Trp
Six to pyruvate	Ala, Cys, Gly, Ser, Thr, Trp
Five to α-ketoglutarate	Arg, Glu, Gln, His, Pro
Four to succinyl-CoA	Ile, Met, Thr, Val
Two to fumarate	Phe, Tyr
Two to oxaloacetate	Asp, Asn

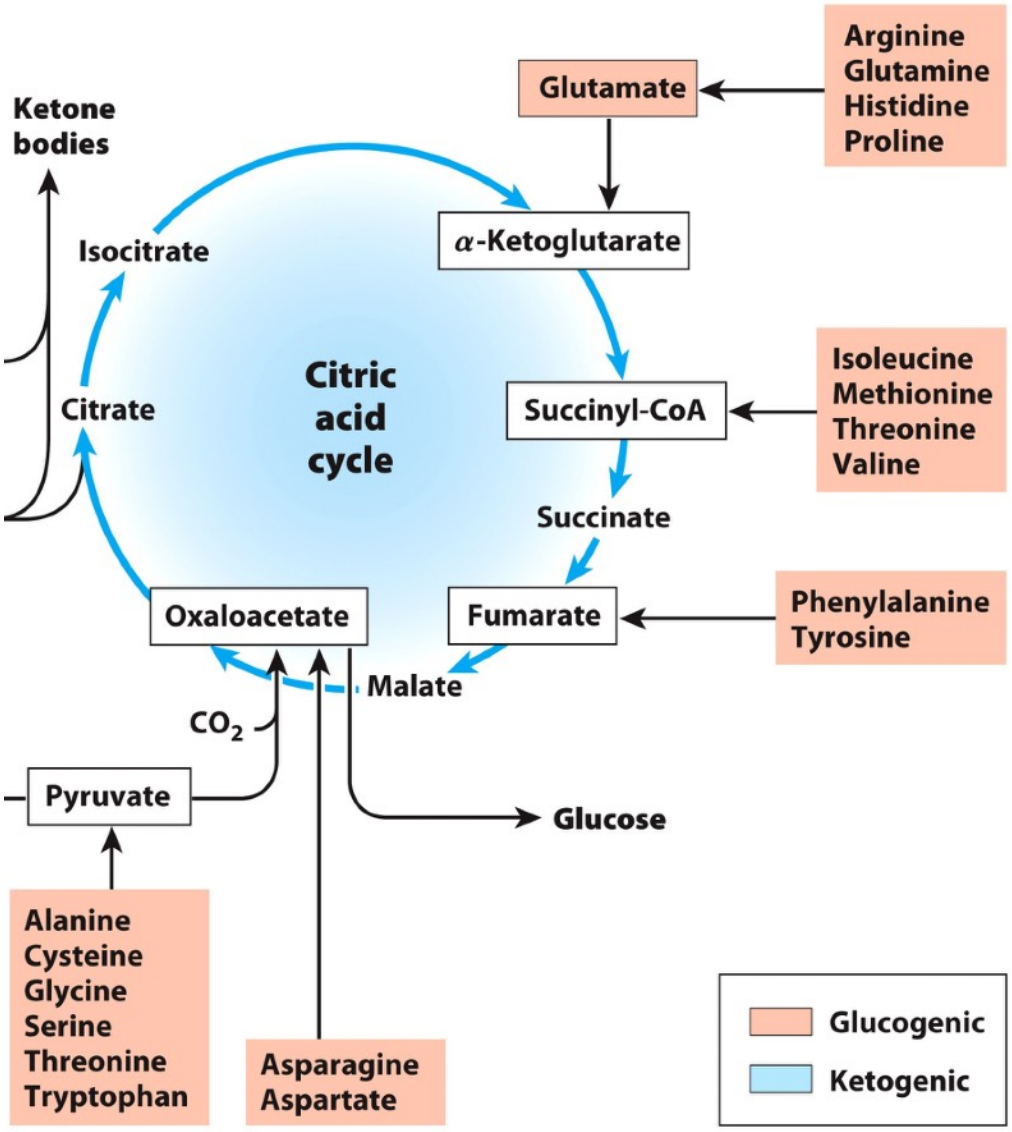
Some Amino Acids -> Ketone Bodies

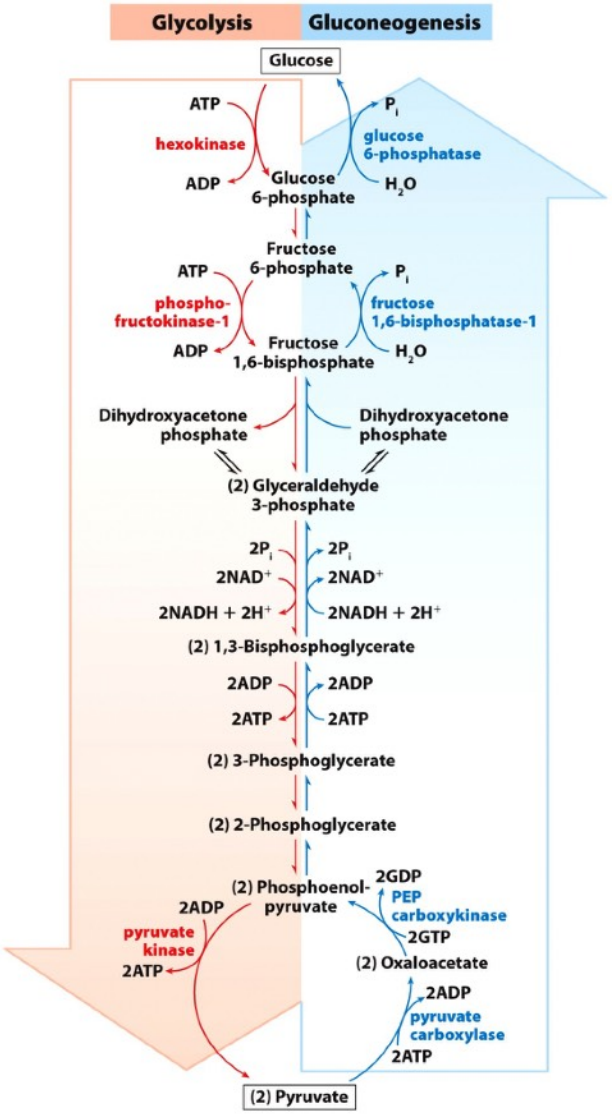


- Degraded to acetyl-CoA or acetoacetyl-CoA.
- Converted to ketone bodies in liver.
- 7 ketogenic amino acids.
  - Three aromatic.
    - Phenylalanine.
    - Tyrosine.
    - Tryptophan.
  - A pair of isomers.
    - Leucine.
    - Isoleucine.
  - Two more.
    - Lysine.
    - Threonine.



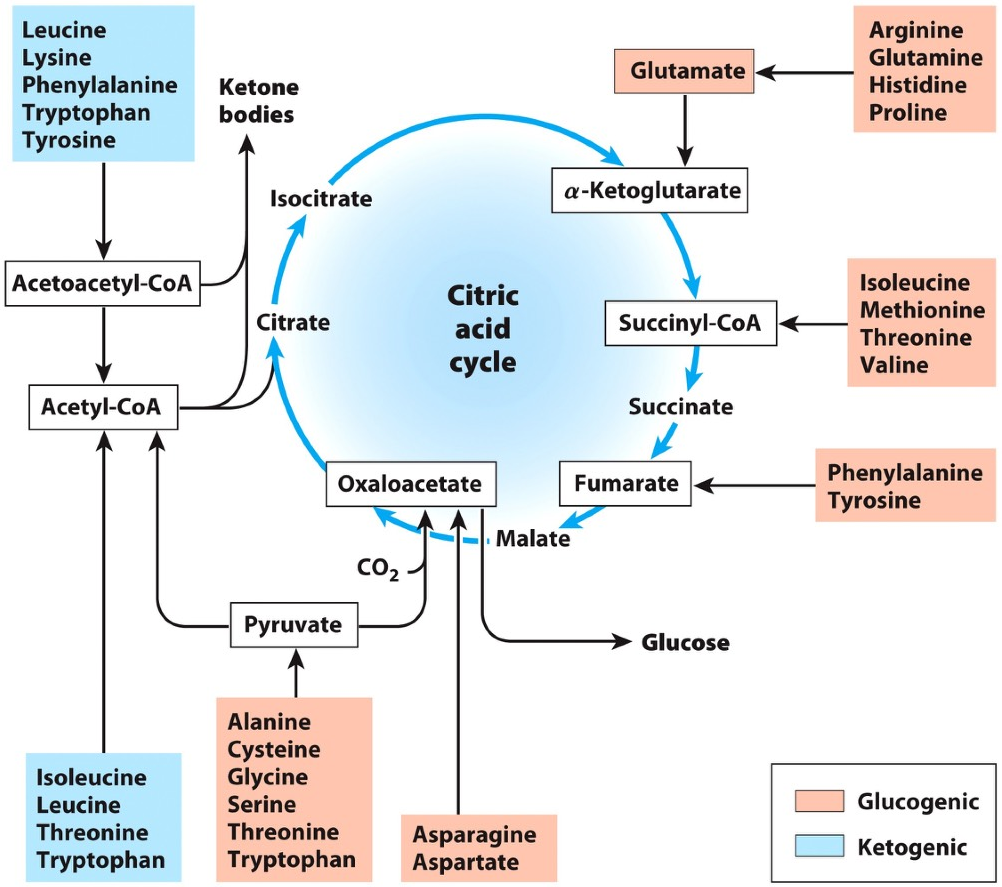
Other Amino Acids -> Glucose





Division NOT Sharp

- Division between ketogenic and glucogenic amino acid NOT sharp.
- Five amino acids are both ketogenic and glucogenic.
  - Phenylalanine and tyrosine.
    - Acetoacetyl-CoA.
    - Fumarate.
  - Tryptophan.
    - Acetoacetyl-CoA.
    - Pyruvate.
  - Threonine and isoleucine.
    - Acetyl-CoA.
    - Succinyl-CoA.
- Two are exclusively ketogenic.
  - Leucine and lysine.



Six Amino Acids -> Pyruvate

①Alanine
- Converted to pyruvate by transamination

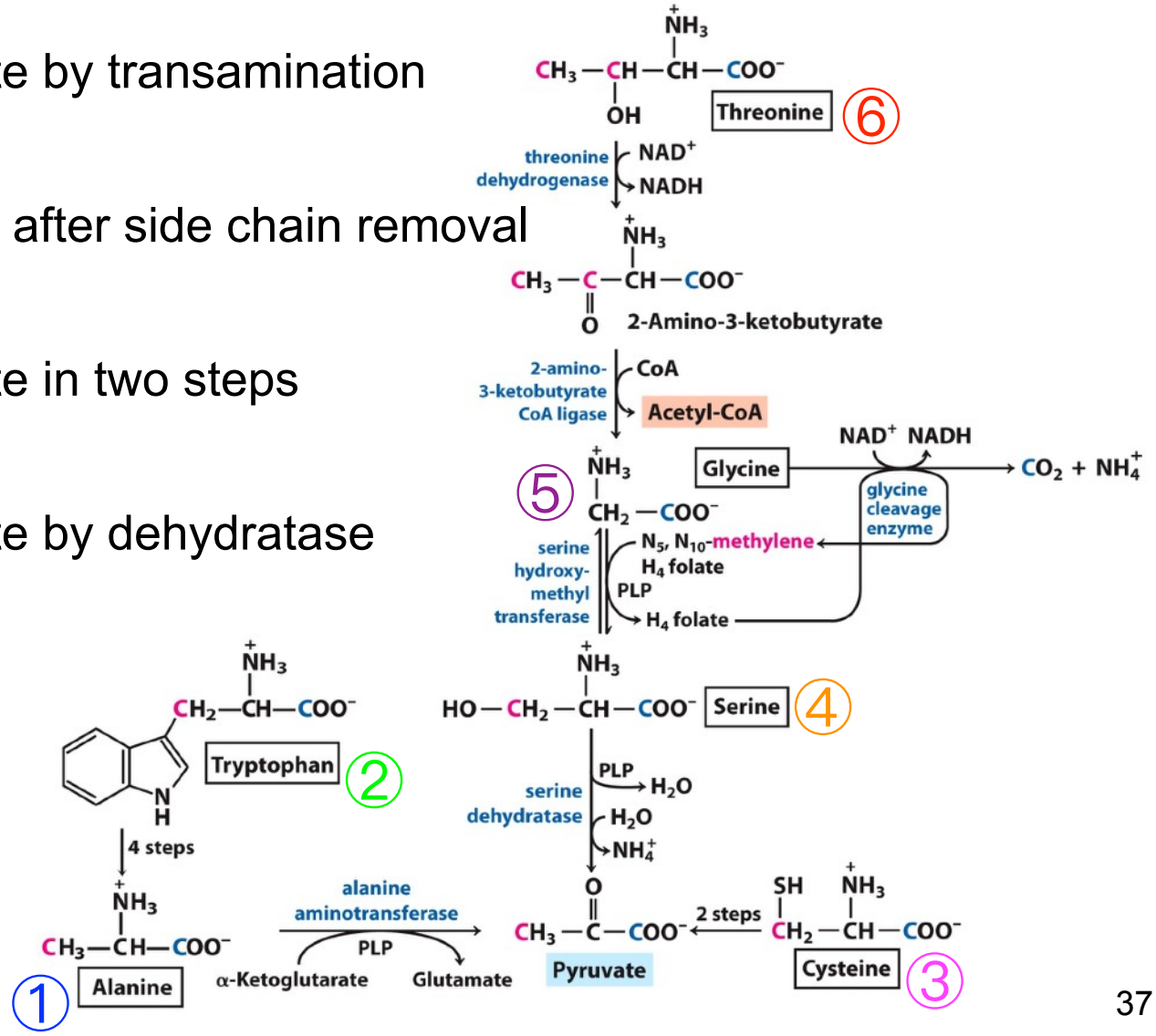
②Tryptophan
- Converted to alanine after side chain removal

③Cysteine
- Converted to pyruvate in two steps

④Serine
- Converted to pyruvate by dehydratase

⑤Glycine
- Converted to serine

⑥Threonine (minor)
- Converted to glycine



Seven Amino Acids -> Acetyl-CoA

①Tryptophan
- To acetoacetyl-CoA

②Phenylalanine
- To tyrosine

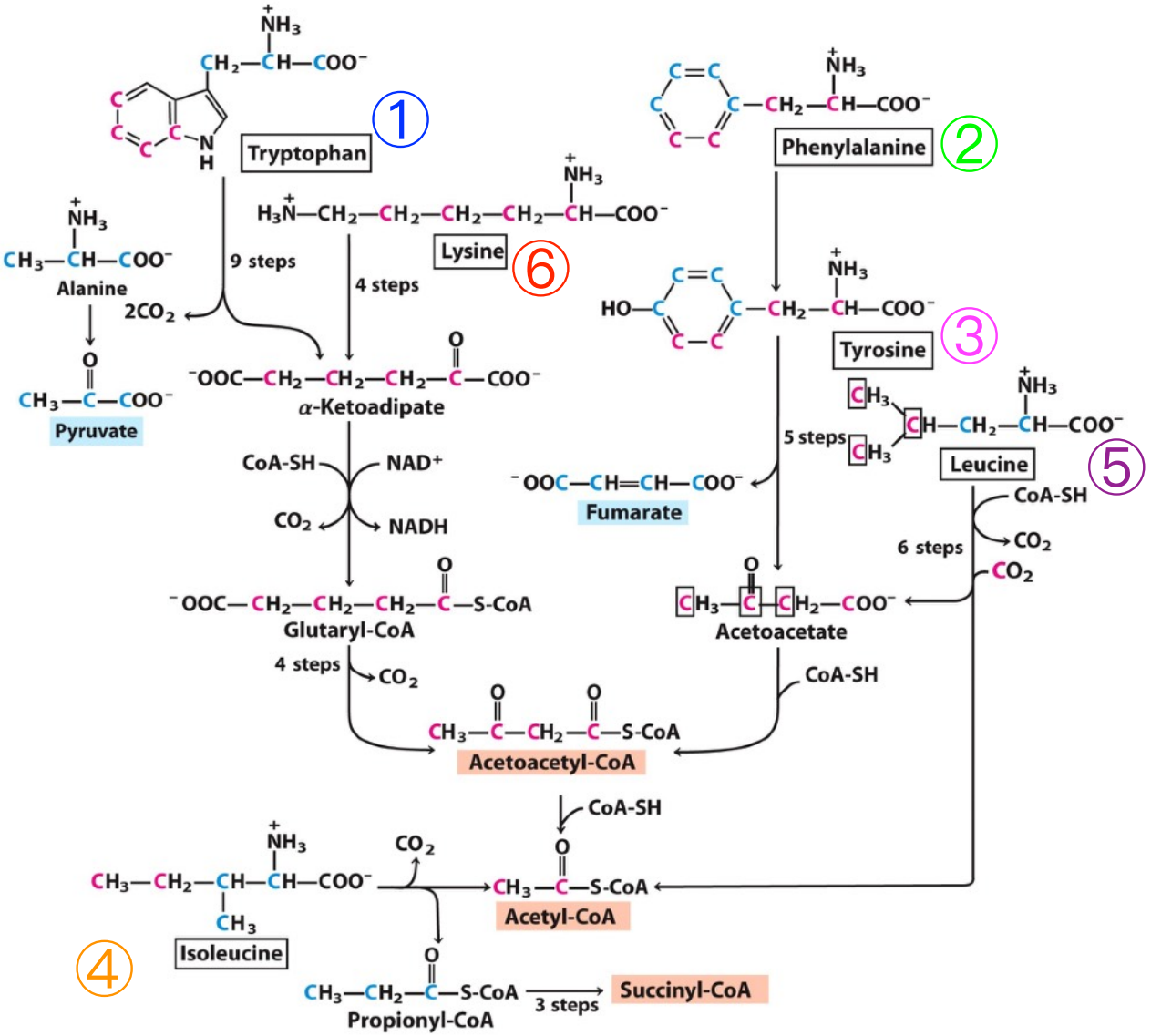
③Tyrosine
- To acetoacetyl-CoA

④Isoleucine
- To acetyl-CoA

⑤Leucine
- To acetoacetyl-CoA and acetyl-CoA

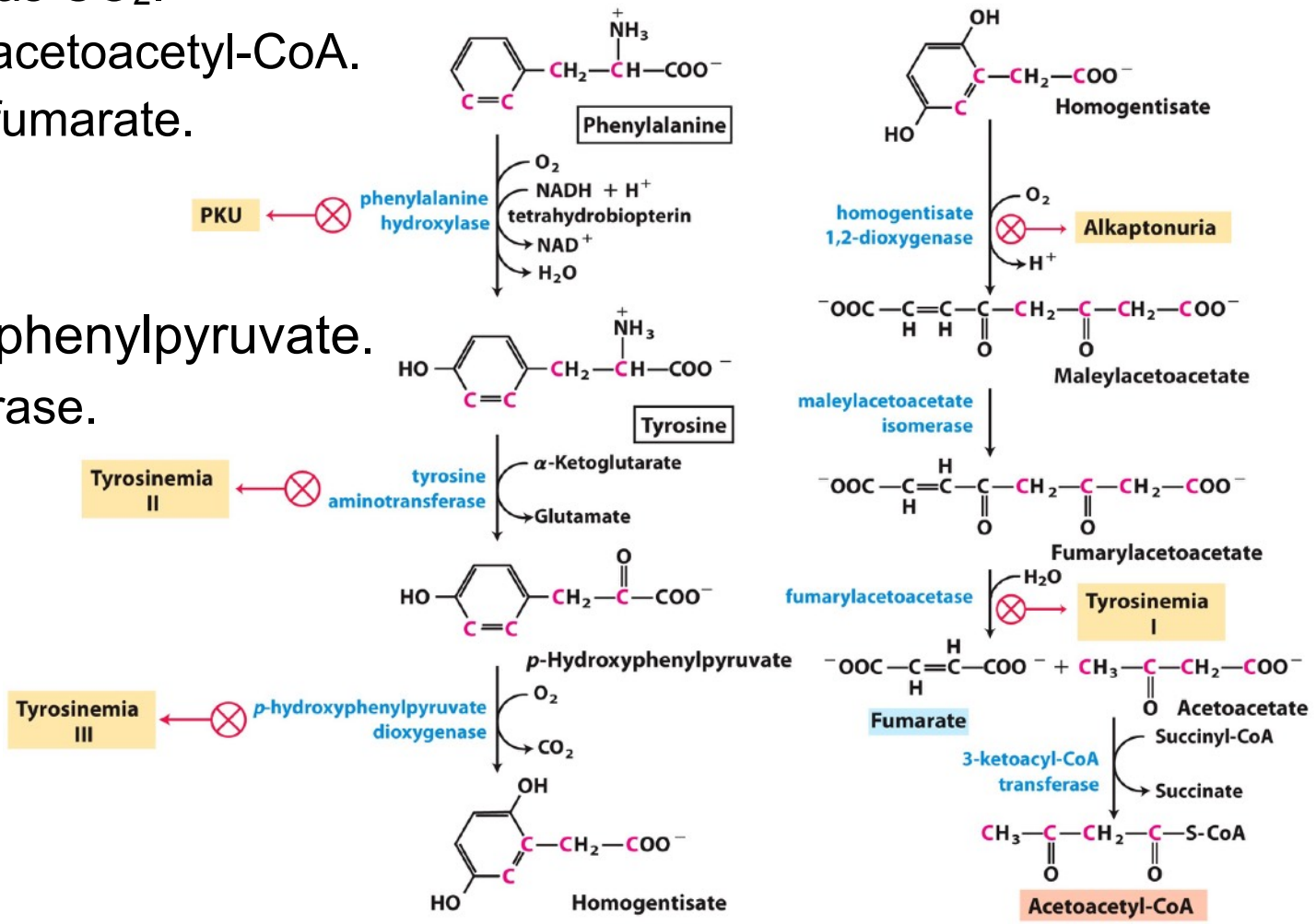
⑥Lysine
- To acetoacetyl-CoA

⑦Threonine
- To acetyl-CoA



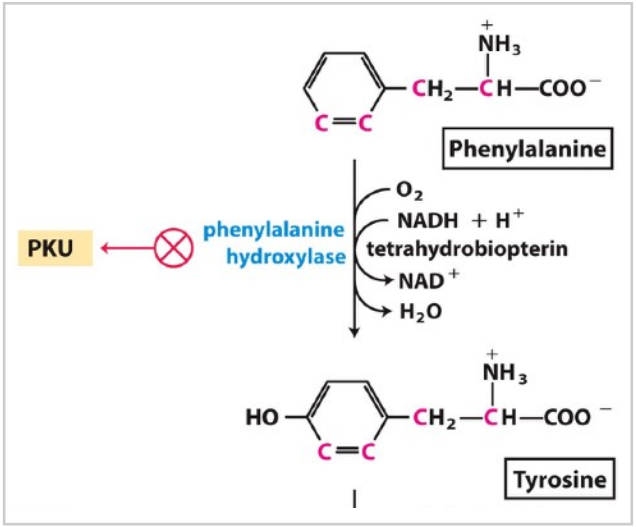
Degradation of Phe and Tyr

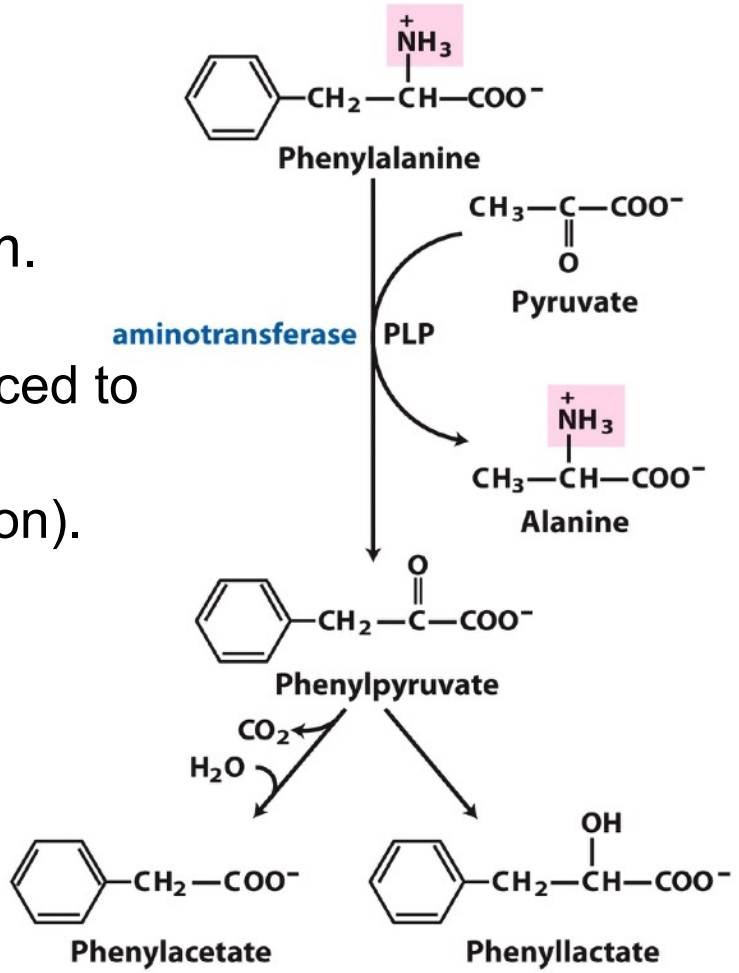
- Phe and Tyr have 9 carbons.
  - 1 carbon lost as CO_2.
  - 4 carbons -> acetoacetyl-CoA.
  - 4 carbons -> fumarate.
- Phe -> Tyr.
  - Hydroxylase.
- Tyr -> hydroxyphenylpyruvate.
  - Aminotransferase.



Phenylketonuria (PKU)

- Caused by inactive Phe hydroxylase.
  - Buildup of Phe in blood.
  - Impairs brain development.
  - Controlled by limited Phe intake.
- A secondary pathway of Phe metabolism.
  - Transamination to phenyl-pyruvate.
  - Decarboxylated to phenyl-acetate or reduced to phenyl-lactate.
  - Characteristic odor of urine (infant detection).





Five Amino Acids -> α-Ketoglutarate

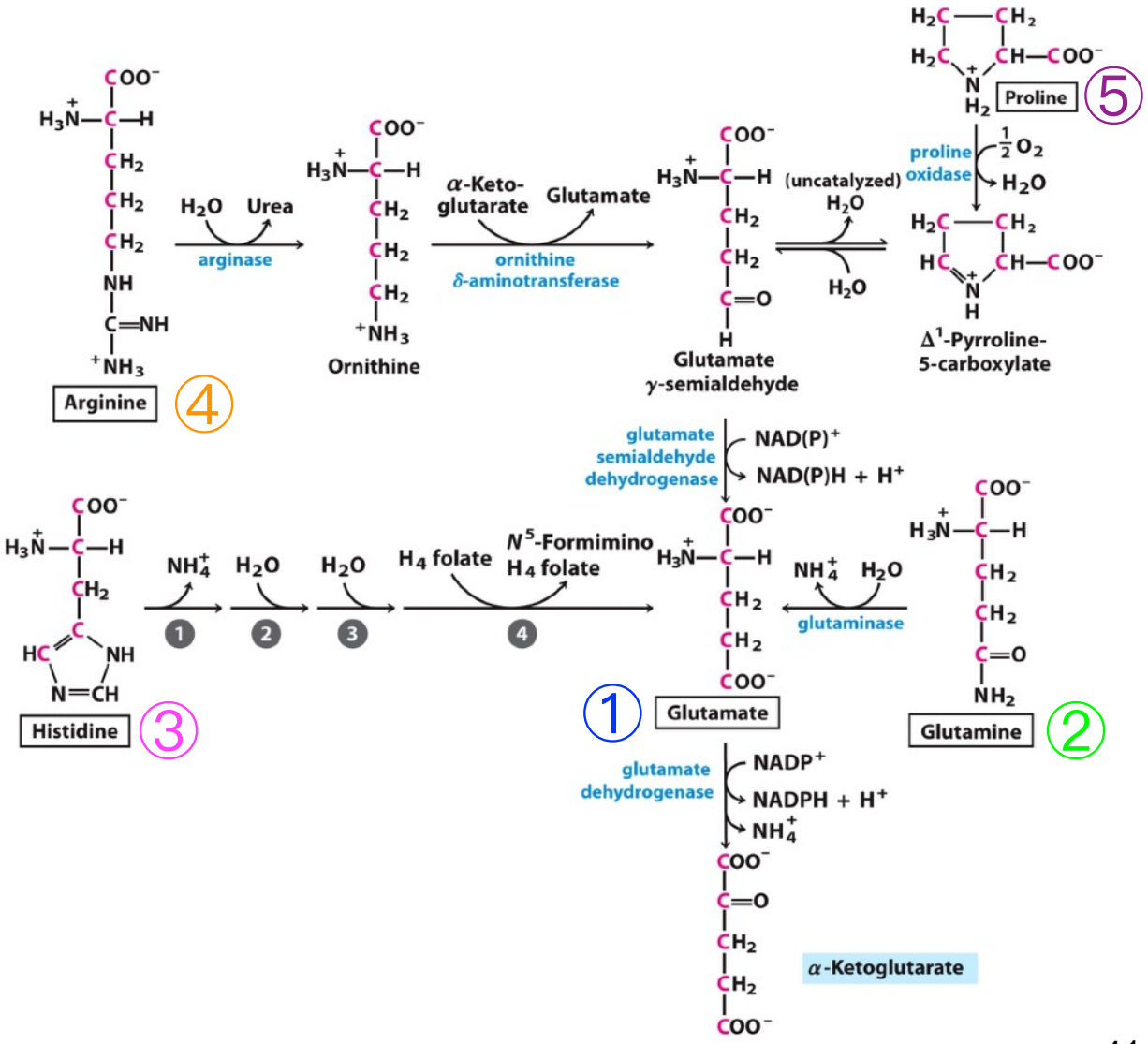
① Glutamate
- To α-ketoglutarate

② Glutamine
- To glutamate

③ Histidine
- To glutamate

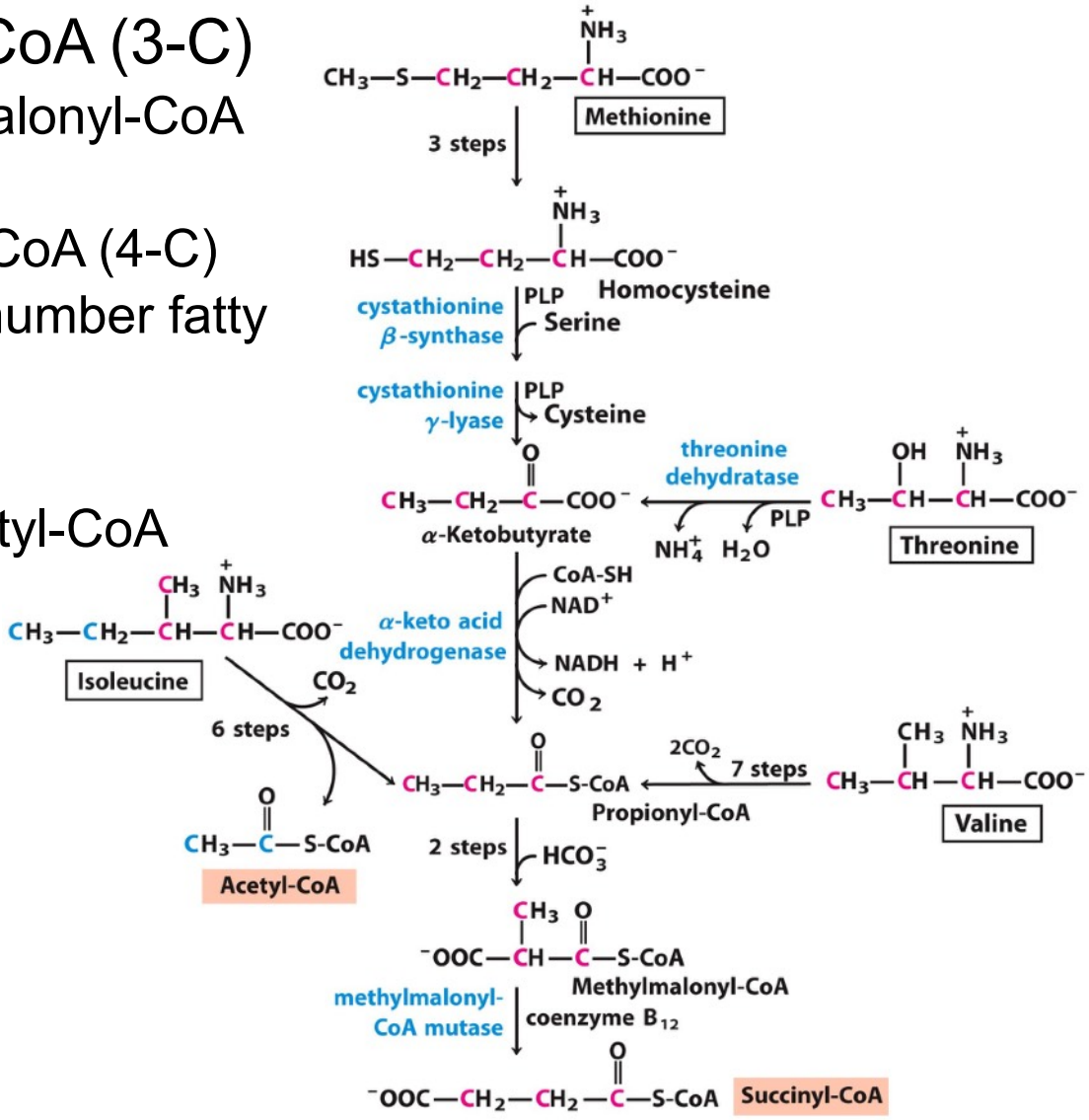
④ Arginine
- To glutamate

⑤ Proline
- To glutamate



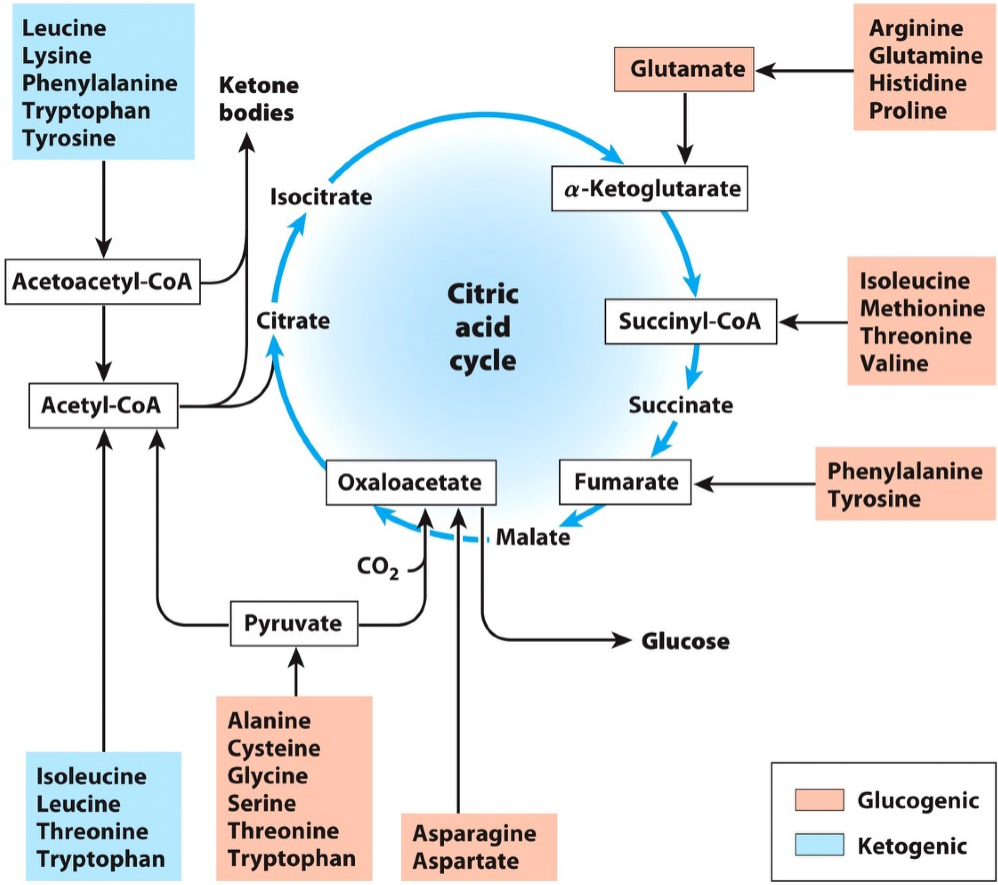
Four Amino Acids -> Succinyl-CoA

- Precursor is propionyl-CoA (3-C)
  - Carboxylation to methylmalonyl-CoA (4-C)
  - Isomerization to succinyl-CoA (4-C)
  - Seen in oxidation of odd-number fatty acid
- Isoleucine
  - To propionyl-CoA and acetyl-CoA
- Valine
  - To propionyl-CoA
- Threonine (major)
  - To propionyl-CoA
- Methionine
  - To propionyl-CoA



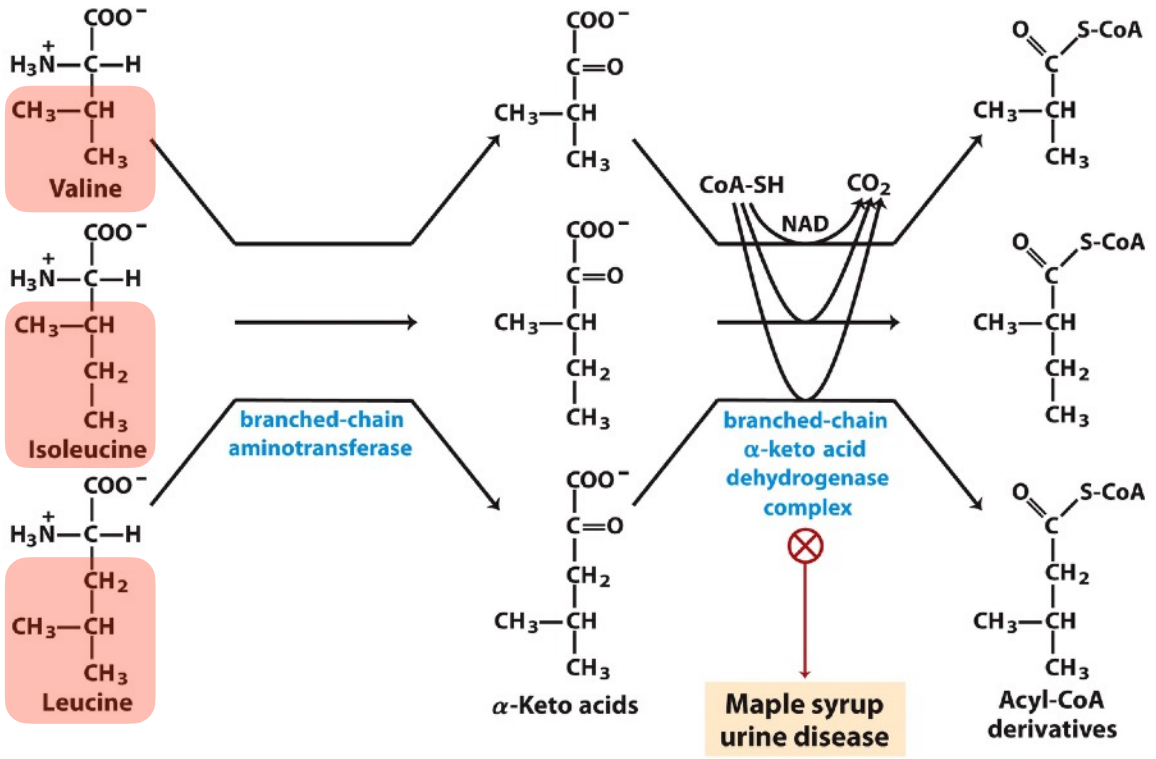
Both Ketogenic And Glucogenic

- Five amino acids are both ketogenic and glucogenic.
  - Phenylalanine and tyrosine (9-C).
    - Acetoacetyl-CoA (4-C).
    - Fumarate (4-C).
  - Tryptophan.
    - Acetoacetyl-CoA (ring).
    - Pyruvate (skeleton).
  - Isoleucine (6-C).
    - Acetyl-CoA (2-C).
    - Succinyl-CoA (4-C).
  - Threonine.
    - Acetyl-CoA (minor via glycine).
    - Succinyl-CoA (major via propionyl-CoA).



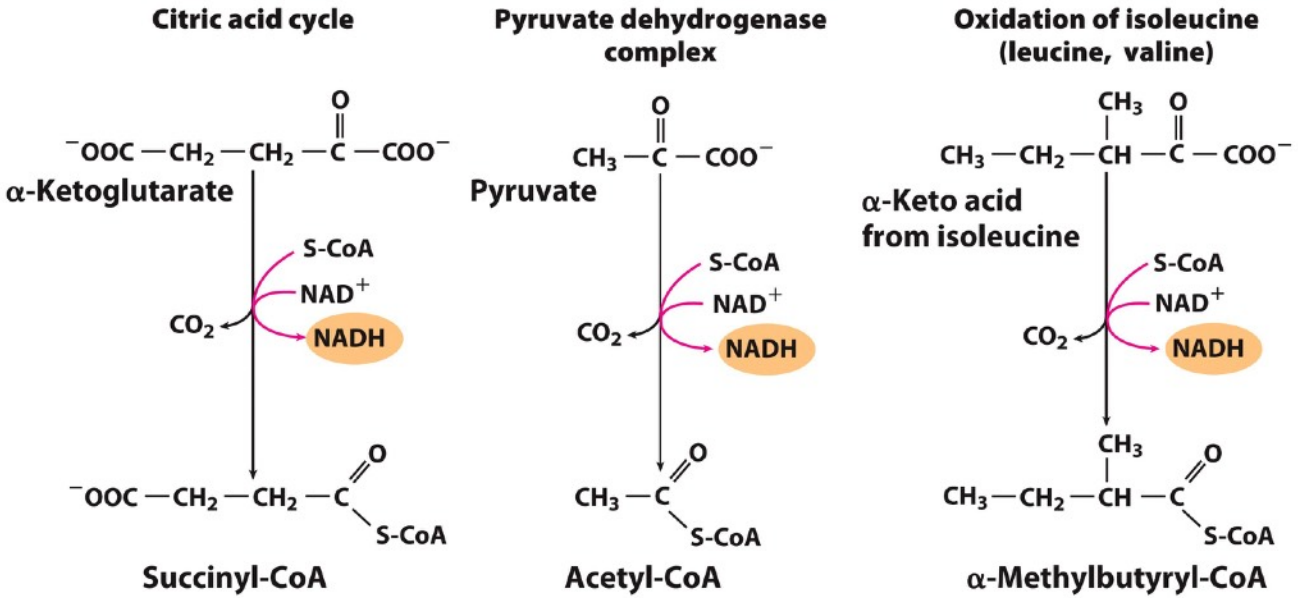
Branched-Chain Amino Acids

- Branched-chain amino acids (Val, Leu, and Ile) are NOT degraded in liver
  - Oxidized as fuel primarily in muscle, adipose, kidney and brain tissues
- Catalyzed by a special aminotransferase NOT present in liver
  - Produce α-keto acid
- Dehydrogenase
  - Produce acyl-CoA



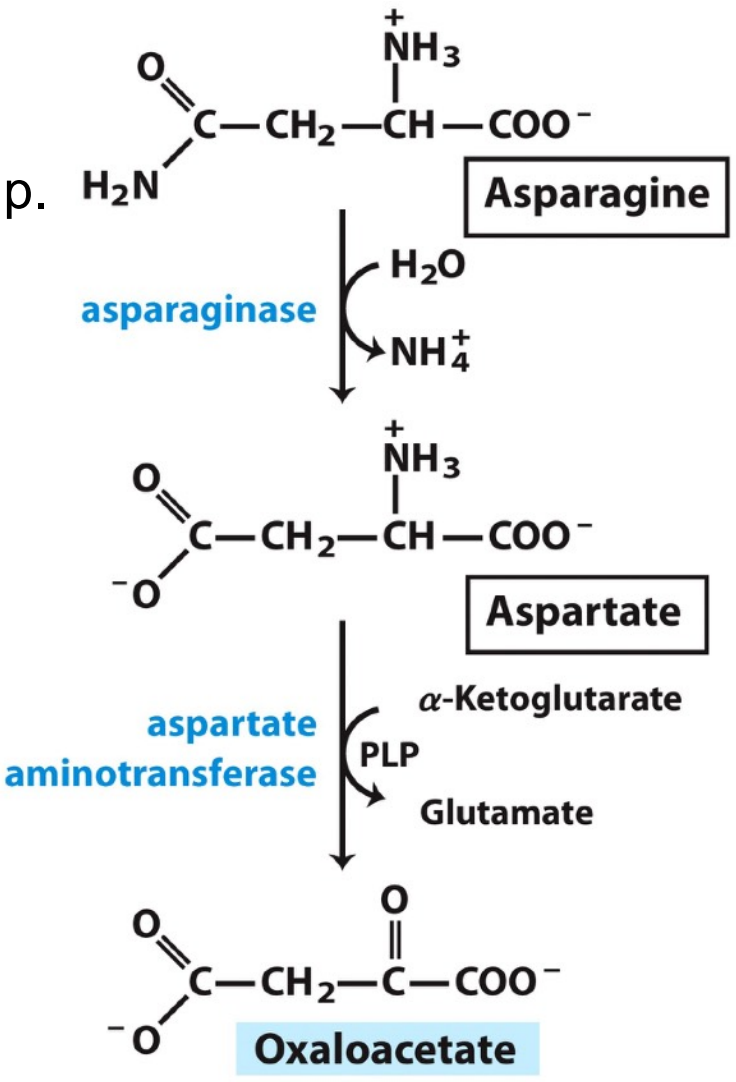
Three Oxidative Decarboxylation Reactions

- Pyruvate -> acetyl-CoA by pyruvate dehydrogenase.
  - Production of acetyl-CoA, which enters citric acid cycle.
- α-ketoglutarate -> succinyl-CoA by α-ketoglutarate dehydrogenase.
  - Production of succinyl-CoA. Step 4 in citric acid cycle.
- α-keto acid -> acyl-CoA by branched chain α-keto acid dehydrogenase.
  - Production of acyl-CoA, which later is converted to acetyl-CoA or succinyl-CoA.



Asp and Asn -> Oxaloacetate

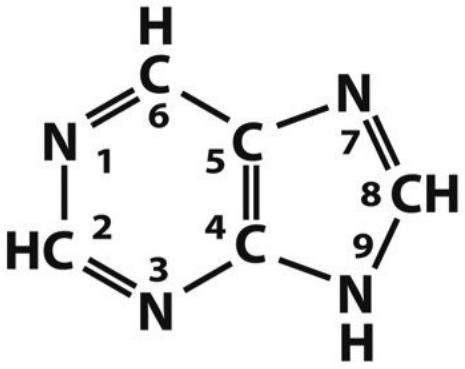
- Asparagine -> aspartate.
  - Catalyzed by asparaginase.
  - Hydrolysis with removal of amino group.
  - Releases ammonia.
- Aspartate -> oxaloacetate.
  - Catalyzed by aminotransferase.
  - Transamination with α-ketoglutarate.
  - Produces glutamate.
- Oxaloacetate in cytosol.
  - Human.
    - Converted to malate in human.
    - Transported to mitochondria.
  - Bacteria.
    - Used directly in citric acid cycle.



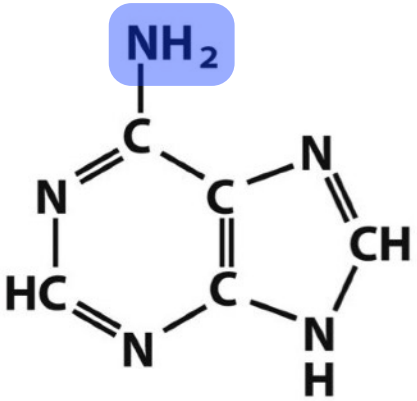
Summary 18.3 Amino Acid Degradation

- Carbon skeletons of amino acids undergo oxidation to CAC intermediates. Depending on degradative end product, some amino acids can be converted to ketone bodies, some to glucose, and some to both.
- Six end products of amino acid catabolism.
  - AWCSGT -> pyruvate.
  - FYWILKT -> acetyl-CoA.
  - EQPHR -> α-ketoglutarate.
  - DN -> oxaloacetate.
  - FY -> fumarate.
  - MITV -> succinyl-CoA.
- Branched-chain amino acids (VIL) are degraded in extrahepatic tissues. PKU is caused by an inactive enzyme which catalyzes conversion of Phe to Tyr.

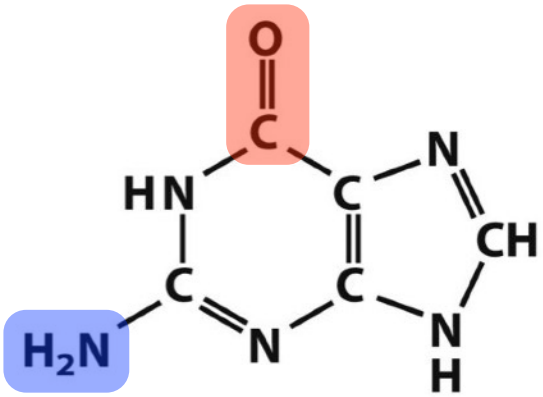
Structures of This Week: Guanine



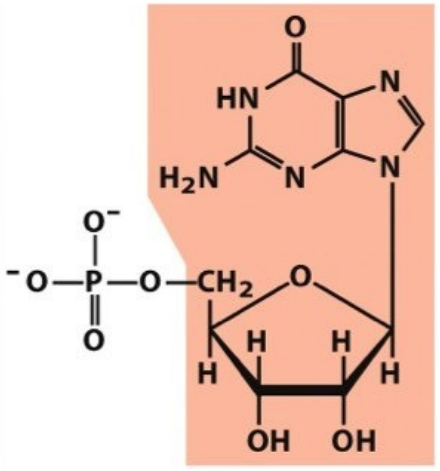
Purine



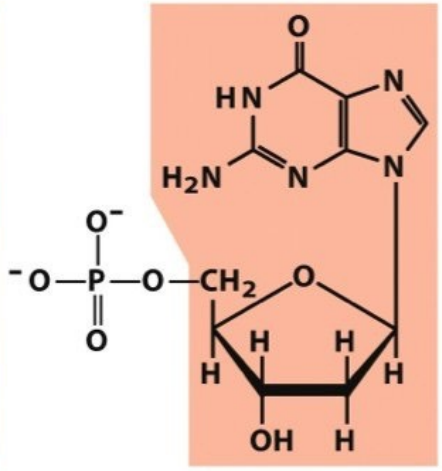
Adenine



Guanine



Guanosine 5’-monophosphate



Deoxyguanosine 5’-monophosphate

Example Question

Which of the following is a zymogen that can be converted to a protease that hydrolyzes peptide bonds adjacent to Lys and Arg residues?

A) Chymotrypsinogen
B) Pepsin
C) Pepsinogen
D) Trypsin
E) Trypsinogen

Example Question

Glutamate is metabolically converted to α-ketoglutarate and NH_4^+ by a process described as:

A) transdeamination
B) hydrolysis
C) oxidative deamination
D) reductive deamination
E) transamination

Example Question

Which substance is *not* involved in the production of urea from NH_4^+ via the urea cycle?

A) Aspartate
B) ATP
C) Carbamoyl phosphate
D) Malate
E) Ornithine

Example Question

In the urea cycle, ornithine transcarbamoylase catalyzes:

A) cleavage of urea to ammonia.
B) formation of citrulline from ornithine and another reactant.
C) formation of ornithine from citrulline and another reactant.
D) formation of urea from arginine.
E) transamination of arginine.

Example Question

Which of the following statements is *false* in reference to the mammalian synthesis of urea?

A) Krebs was a major contributor to discovery of urea cycle.
B) The amino acid arginine is the immediate precursor to urea.
C) The carbon atom of urea is derived from HCO_3^-.
D) The precursor to one of the nitrogens of urea is aspartate.
E) The process of urea production yields energy.

Example Question

Serine or cysteine may enter the citric acid cycle as acetyl-CoA after conversion to:

A) oxaloacetate.
B) propionate.
C) pyruvate.
D) succinate.
E) succinyl-CoA.

Example Question

Which of these amino acids are converted to α-ketoglutarate?

1. Glycine
2. Glutamate
3. Histidine
4. Arginine
5. Proline

A) 1, 3, and 5
B) 2, 3, and 4
C) 2, 3, and 5
D) 2, 3, 4, and 5
E) 3, 4, and 5

Example Question

Which of these amino acids are converted to succinyl-CoA?

1. Isoleucine
2. Valine
3. Methionine
4. Arginine
5. Threonine

A) 2 and 4
B) 2, 3, and 4
C) 2, 4, and 5
D) 1, 4, and 5
E) 1, 2, 3, and 5

Example Question

Which of these amino acids are converted to oxaloacetate?

1. Asparagine
2. Glutamine
3. Serine
4. Arginine
5. Aspartate

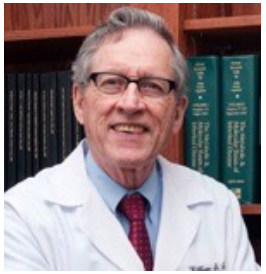
A) 2 and 4
B) 2, 3, and 4
C) 2, 4, and 5
D) 1 and 5
E) 1, 3, and 5

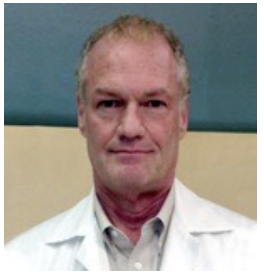
Example Question

In the treatment of diabetes, insulin is given intravenously. Why can't this hormone, a small protein, be taken orally?

Forensic Files S03E08 Deadly Formula

- The Stallings Family.
  - Father and mother: David and Patricia.
  - Two sons: Ryan and David Junior (DJ).
- Two Hospitals and one lab.
  - St. Louis Children's Hospital.
  - Cardinal Glennon Children's Hospital.
  - SmithKline Beecham Clinical Laboratory.
- Two prosecutors.
  - John Appelbaum.
  - George McElroy.
- Three scientists.
  - William Sly and James Shoemaker.
  - Piero Rinaldo.





Methylmalonic acidemia (MMA)

- Methylmalonyl-CoA mutase is defective.
  - Involved in catabolism of 4 amino acids (MITV) and odd-number fatty acids.
  - Could NOT convert methylmalonyl-CoA to succinyl-CoA.
  - Converted to methylmalonic acid instead, which accumulates in blood.
- MMA symptoms almost identical to ethylene glycol poisoning.
  - Mother charged with first degree murder and sentenced to life in prison.
  - Original lab reports was considered "scary" by Yale SOM expert.
  - "NOT a questionable interpretation. Quality of analysis was UNACCEPTABLE."