Amino Acid Metabolism

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OBJECTIVES

After studying the material presented in this lecture, the student will be able to know:

1. Amino acids are important sources for energy
2. Amino acids are the precursors of many essential bioactive amines
3. Excess NH_3 produced during the metabolism of amino acids is excreted as Urea formed in the Urea cycle
4. Some amino acids are ketogenic, some are glucogenic and some are both
5. Many metabolic diseases are the result of abnormal Amino Acid Metabolism

RECOMMENDED READING

Lehninger, Principles of Biochemistry, 5th edition, Chapter 18
Marks' Medical Biochemistry, Section 7

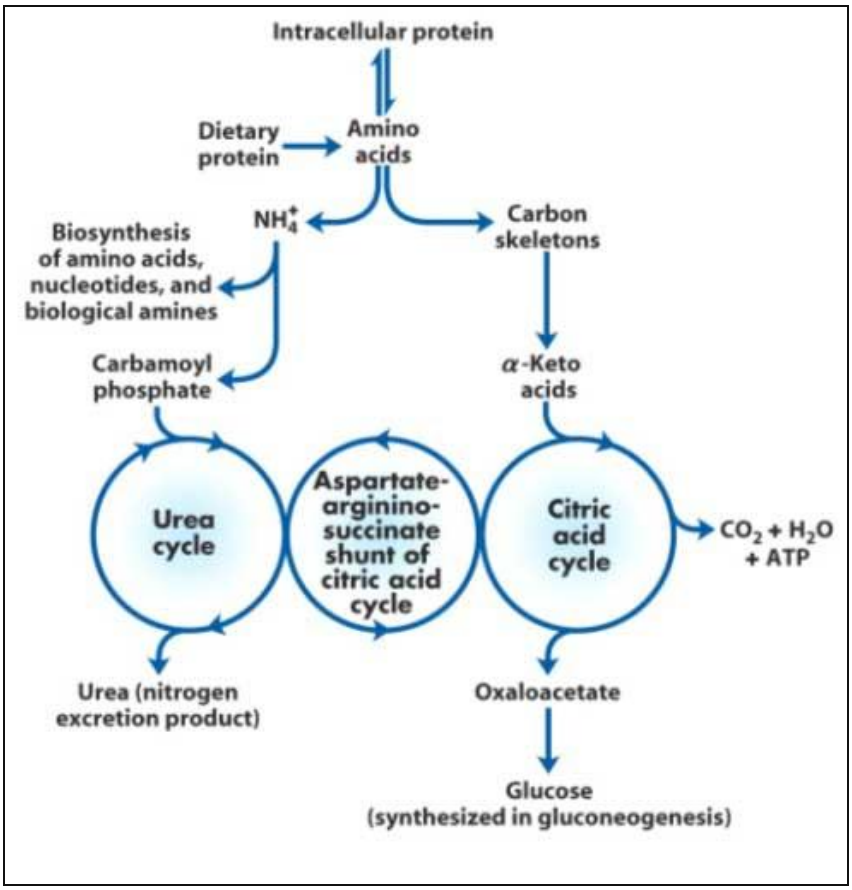
Introduction and Summary of topics to be covered:

Overviews
Amino Acids as a source of energy
Digestion; the 1st step in the process
The 3 general reactions
Removal of the NH_3 group
Removal of the Carboxyl group
Transfer of Methyl groups

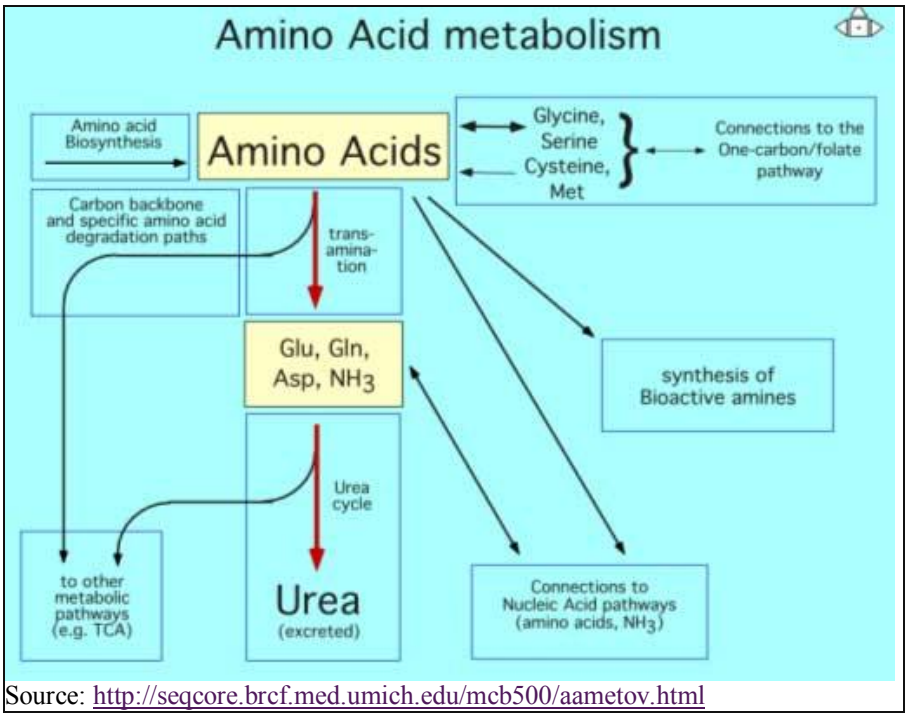
Specific pathways for amino acid carbon metabolism
One carbon metabolism
Metabolic processing of amino acid nitrogen
The Urea Cycle
Phosphocreatine, an important energy reservoir

I. OVERVIEW

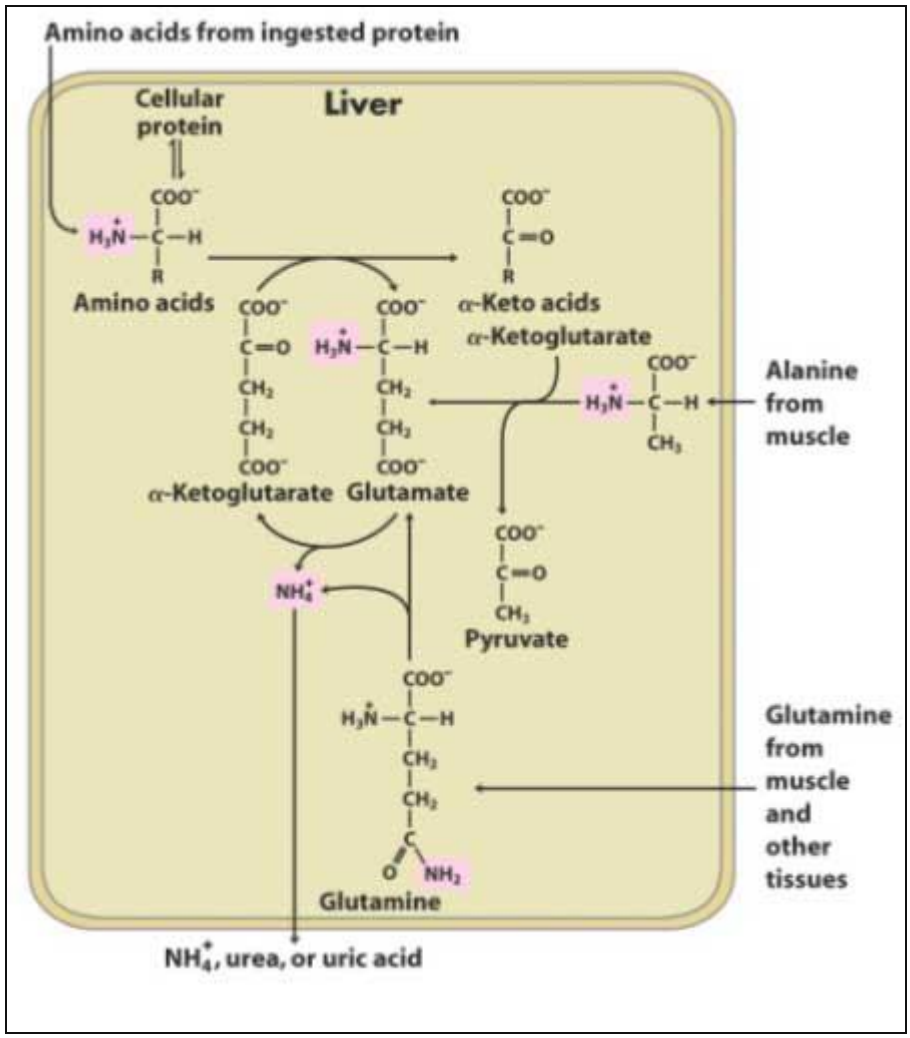
Amino acids from protein in the diet or from intracellular protein can be metabolized to provide a significant contribution to the generation of energy. (Fig. 18-1 & 2)



Additional schemes depicting the central role of Amino Acids in many biological pathways.



Source: http://seqcore.brcf.med.umich.edu/mcb500/aametov.html



Contribution to metabolic energy varies depending on the organism.

Carnivores may obtain up to **90%** of energy requirements from amino acid metabolism

Vegetarians may obtain only a small fraction of their energy needs from amino acids.

Microorganisms can also use amino acids for an energy source if they are present in their environment.

Plants using photosynthesis for energy rarely, if ever, use amino acids for energy.

In animals, amino acids undergo **oxidative degradation** during 3 different metabolic circumstances.

During normal synthesis & degradation of cellular proteins… some amino acids will undergo oxidative degradation if they are not needed for new protein.

If a person has a diet rich in protein and has excess amino acids, they can not be stored and will be degraded. For example, people on the **Atkins** diet eat abundant amounts of protein and very little carbohydrates.

During starvation or in patients with diabetes when carbohydrates are not available for energy, then protein must be used for an energy source.

Under these different circumstances, amino acids lose their amino groups forming alpha-keto acids, which in turn undergo oxidation to CO_2 and water. In the process ammonia is also generated and is available for the biosynthesis of amino acids, nucleotides and other biological amines. In addition, the carbon skeleton can eventually be converted to glucose through the **citric acid cycle** to provide energy.

NOTE: When protein is broken down for **ENERGY**, then most of the energy is derived from **the Oxidation of Alpha Keto Acids** derived from the amino acids.

II. DIGESTION

Dietary Protein is Enzymatically Degraded to Amino Acids in the Digestive System.

Chewing the food and mixing with **Saliva** starts the process of digestion.

A. Functions of Saliva

1. Digestion
   Bolus Formation
   Lubrication
   Dissolves Food
   Aids in Taste
2. Protection
3. Soft Tissue Repair
4. Moistens Mouth & Throat
5. Aids in Speech

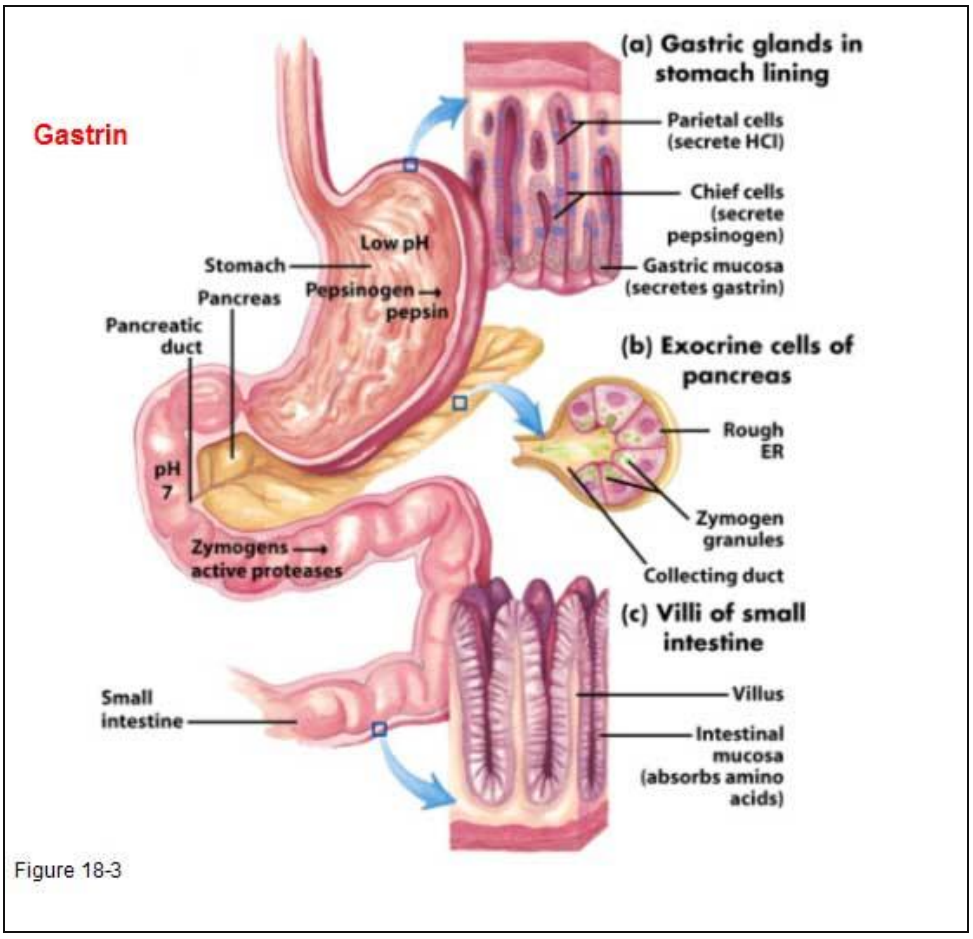


Figure 18-3

Gastrin: when food enters the stomach, the gastric mucosa secretes the hormone Gastrin that in turn stimulates secretion of HCl by the **parietal cells** of the gastric glands.

Pepsinogen secretion from the Chief cells is also stimulated by Gastrin and it is converted from this inactive, **"zymogen"** form to active **Pepsin**

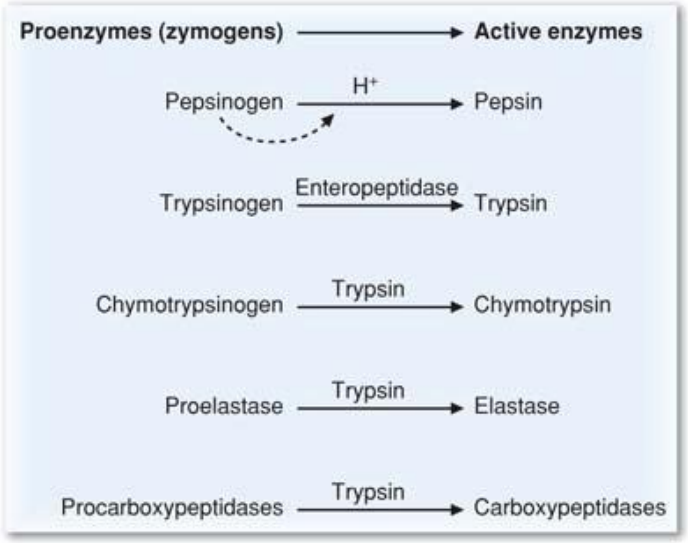
Gastric juice… kills bacteria, other foreign cells and denatures the protein thus exposing any internal peptide bonds.

Proteins are cleaved on the **amino**-terminal side of aromatic amino residues Tyrosine, Phenylalanine and Tryptophan by **Pepsin**. As the contents pass into the small intestine, the pancreas secretes bicarbonate to neutralize the acid and allow other protein degrading enzymes to function.

Secretin: produced in the upper portion of the small intestine (duodenum) and inhibits gastric acid secretion & stomach motility; stimulates the pancreas to release bicarbonate ions and stimulates the gall bladder to secrete bile.

The zymogen **Trypsinogen** is converted to the active protease called **Trypsin** by an enzyme called **enteropeptidase**. **Trypsin** then cleaves proteins at sites of Lysine and Arginine on the

carboxy-terminal side. Chymotrypsinogen is converted to Chymotrypsin by Trypsin. The **Chymotrypsin** then cleaves on the carboxy-terminal side of Tyrosine, Phenylalanine and Tryptophan. **Elastase** is formed from Proelastase by the action of Trypsin and then cleaves proteins at bonds in which the carboxyl group is contributed by small side chain amino acids (alanine, glycine & serine). **Carboxypeptidases** are "broad spectrum" enzymes and make multiple hits on remaining small peptides.



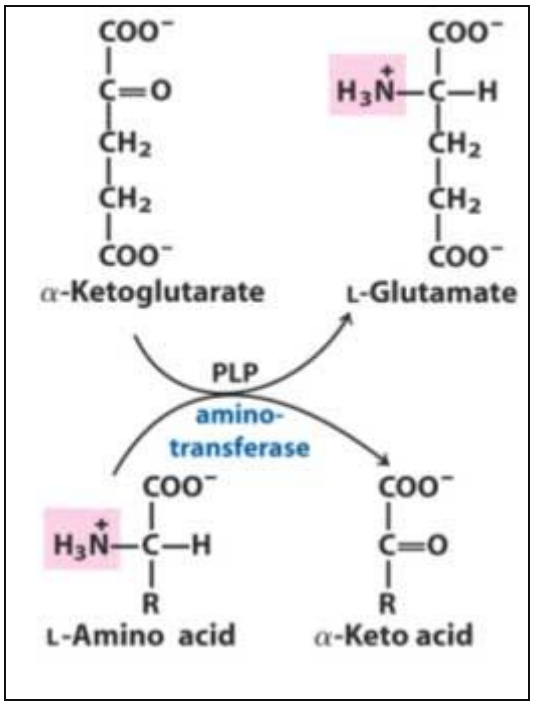
Clinical Note: Acute Pancreatitis… Duct is obstructed and the zymogens are converted to active enzymes and attack the pancreas itself; This can be fatal.

Non-Essential and Essential Amino Acids.	
Non-Essential	**Essential** (Pvt. Tim Hall)
Alanine	Phenylalanine
Asparagine	Valine
Asparate	Tryptophan
Cysteine	Threonine
Glutamate	Isoleucine
Glutamine	Methionine
Glycine	Histidine
Proline	Arginine*
Serine	Leucine
Tyrosine	Lysine
* Essential for young, growing animals, but not in adults.	

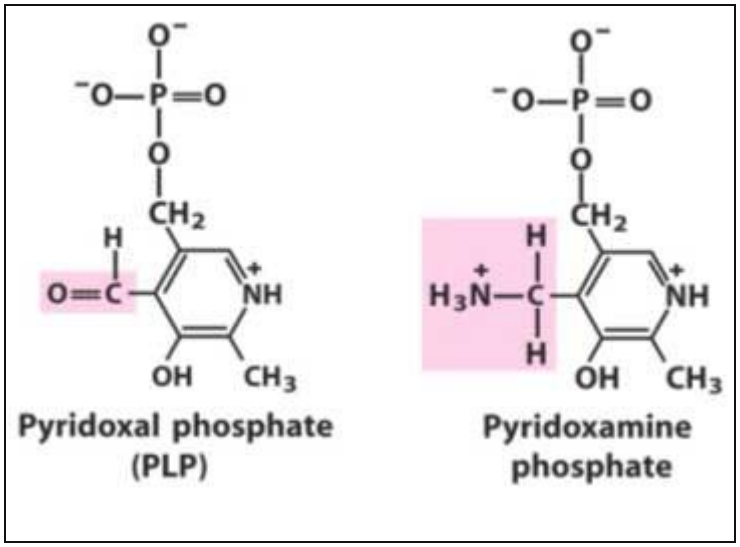
III. **THREE GENERAL REACTIONS responsible for Amino Acid metabolism; Those involving the <u>Amino Group</u>; those involving the <u>Carboxyl Group</u> and those involving the <u>Methyl Group</u>.**

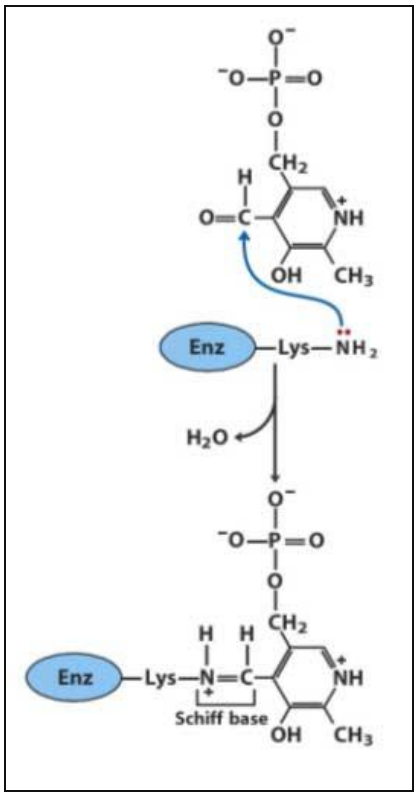
A. **Reactions involving the Amino Group:**

1. **Transamination**
   a. **Reaction.** Catalyzed by enzymes called **aminotransferases** or **transaminases**.



   b. **Mechanism** Pyridoxal phosphate (PLP) is the co-factor for this class of reactions called **Transaminations**. PLP is related to Vitamin B6

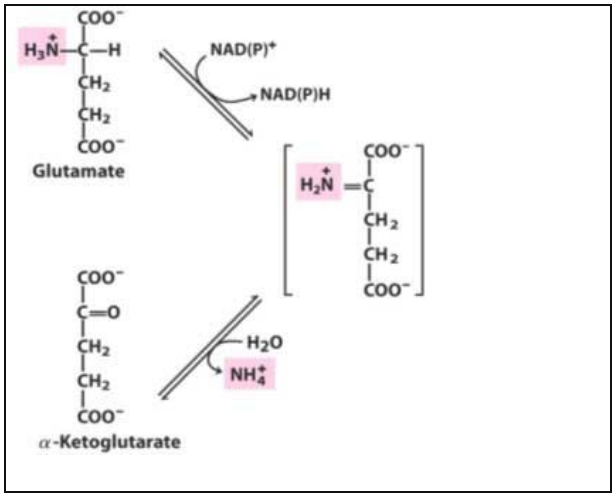




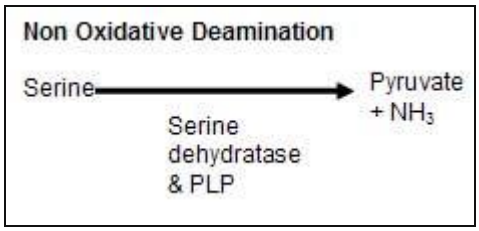
c. The amino group is transferred to the alpha carbon of alpha-ketoglutarate leaving behind the alpha keto acid analog of the amino acid.

2. **Deamination**

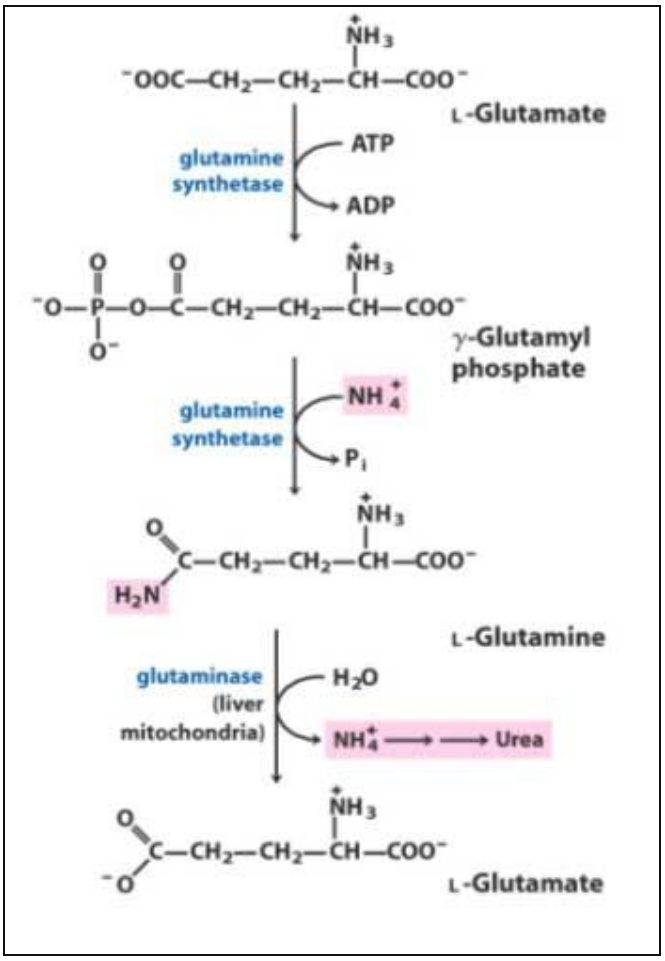
a. **Oxidative**. Glutamate is transported from the cytosol to the mitochondria where it undergoes **Oxidative Deamination** catalyzed by **L-glutamate dehydrogenase** and alpha ketoglutarate and ammonia ($\mathbf{NH_4^+}$) are produced.



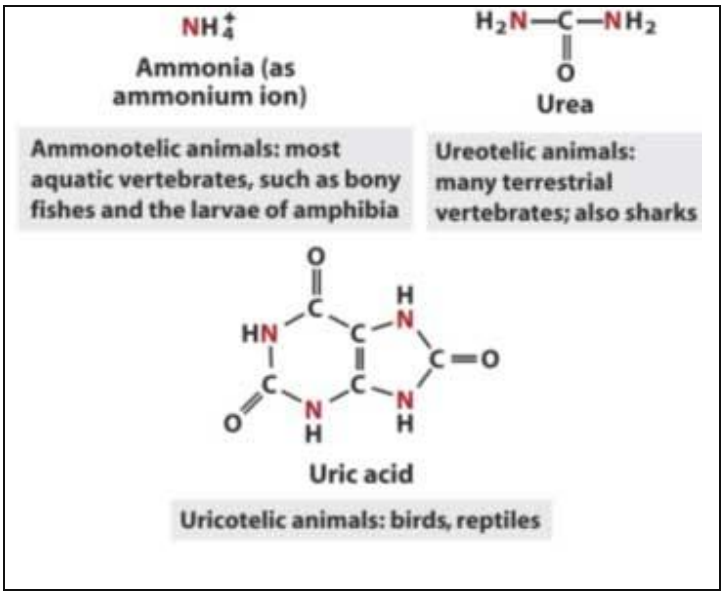
b. **Non-Oxidative Deamination**. The enzymatic conversion of Serine to Pyruvate +NH3 is an example of this type of reaction. This is a **Dehydration** reaction with no net change in oxidation but results in the release of NH_3.



3. **Deamidation: Direct removal of an Amide functional group. An example would be the second half of the reaction below.**

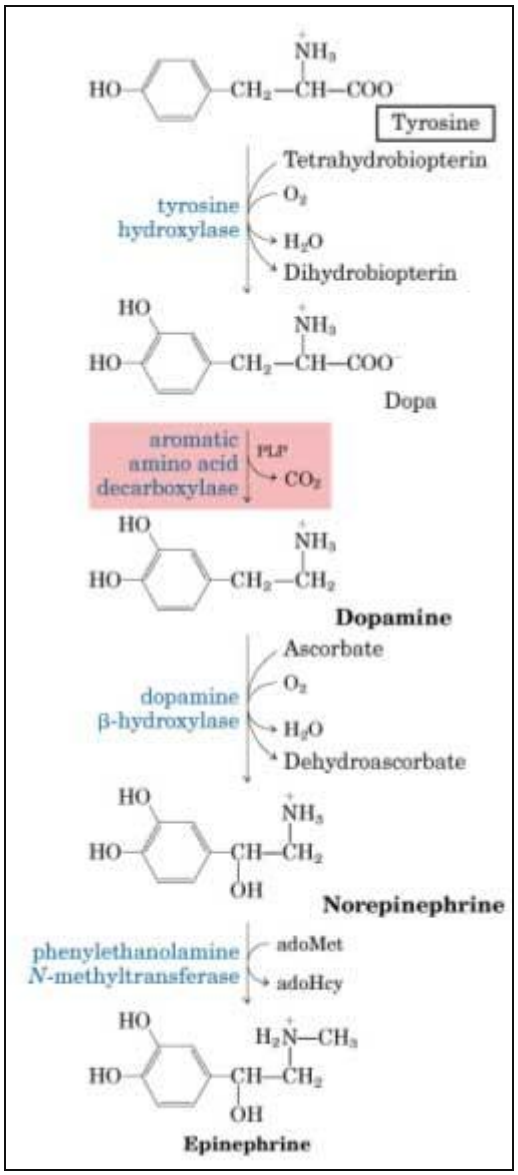


The **Glutamate** that is formed channels these amino groups into biosynthetic pathways or into terminal pathways where the nitrogenous wastes are eliminated as Ammonia or Urea.



B. **Decarboxylation** Amino Acids can be converted into important biological **amines** by the process of **Decarboxylation**.

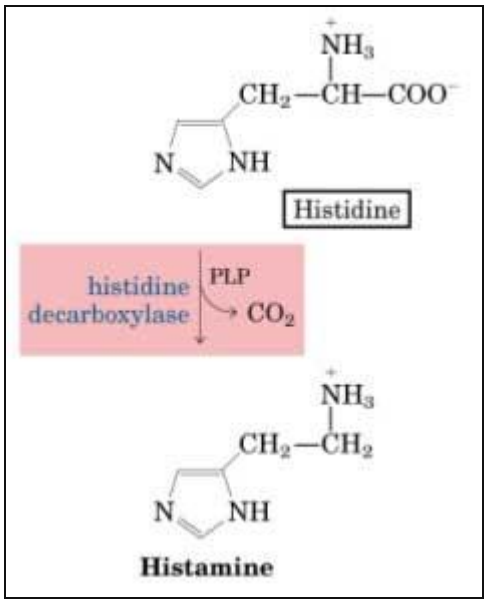
For example; Catecholamine Neurotransmitters are formed by this reaction. (Dopamine, Norepinephrine, Epinephrine) Histamine, Serotonin, Spermidine & Spermine.



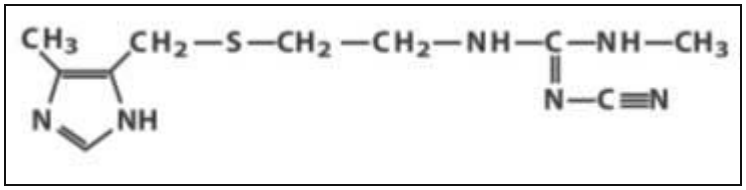
General Reaction. Specific decarboxylases, utilizing PLP as a co-factor, remove the carboxyl group from the amino acid thus forming a new biological amine and liberating CO_2.

Clinical Note: Recently it has been reported that patients with Alzheimer's disease & Parkinson's disease have reduced levels of Dopamine. Overproduction of Dopamine in the brain may be linked with psychological disorders such as schizophrenia.

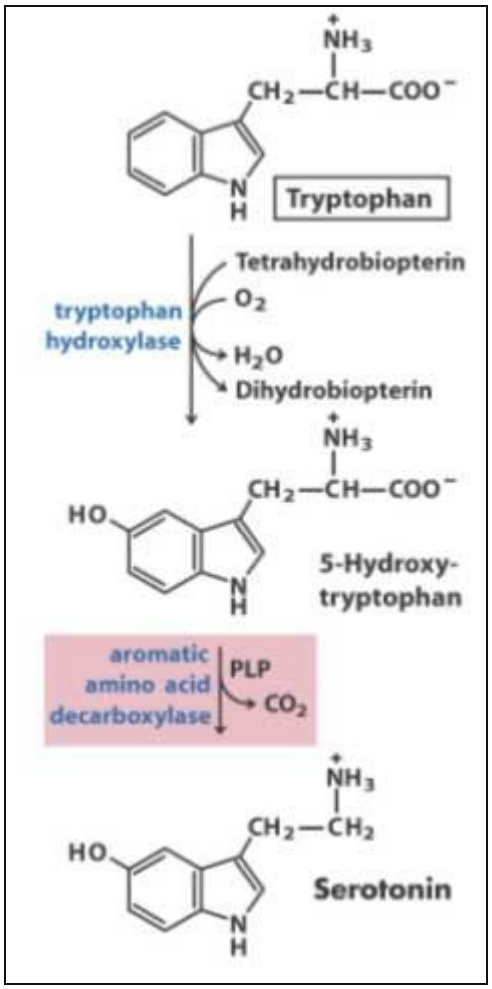
Once again, Histamine is formed from Histidine by this **General Reaction of Decarboxylation**. Specific decarboxylases, utilizing PLP as a co-factor, remove the carboxyl group from the amino acid thus forming a new biological amine and liberating CO_2.



Clinical Note: Histamine stimulates acid secretion in the stomach. **Cimetidine** (Tagamet), an H_2 receptor antagonist and an **analog** of Histamine is used to treat duodenal ulcers because it blocks gastric acid secretion.



Serotonin and Melatonin (not shown) are also formed from tryptophan by Decarboxylation reactions.

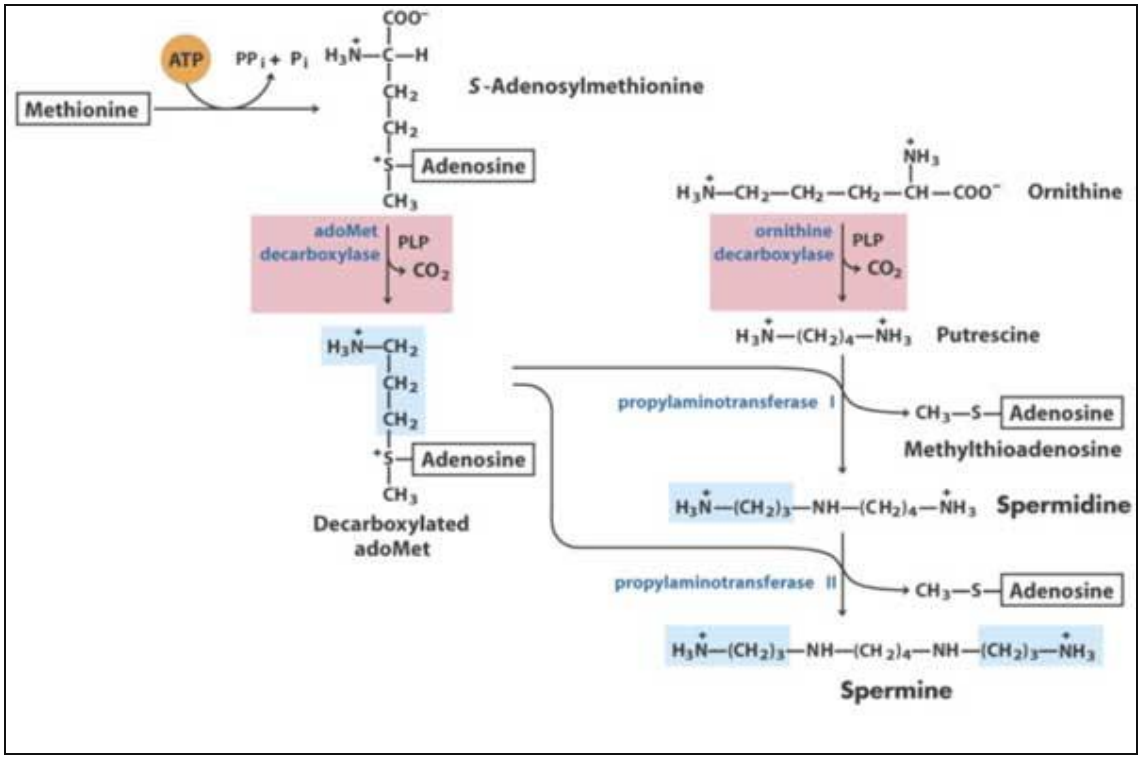


Clinical Note: Serotonin is a neurotransmitter in the brain and causes contraction of smooth muscle of arterioles and bronchioles. Melatonin is a "sleep inducing" molecule. Ingestion of foods rich in Tryptophan (meat & milk) leads to sleepiness because the resulting serotonin is also sleep-inducing. Tryptophan also reduces anxiety & depression and has been called "Nature's Prozac". Turkey meat is especially rich in Tryptophan and is the cause for that very tired feeling after Thanksgiving dinner….

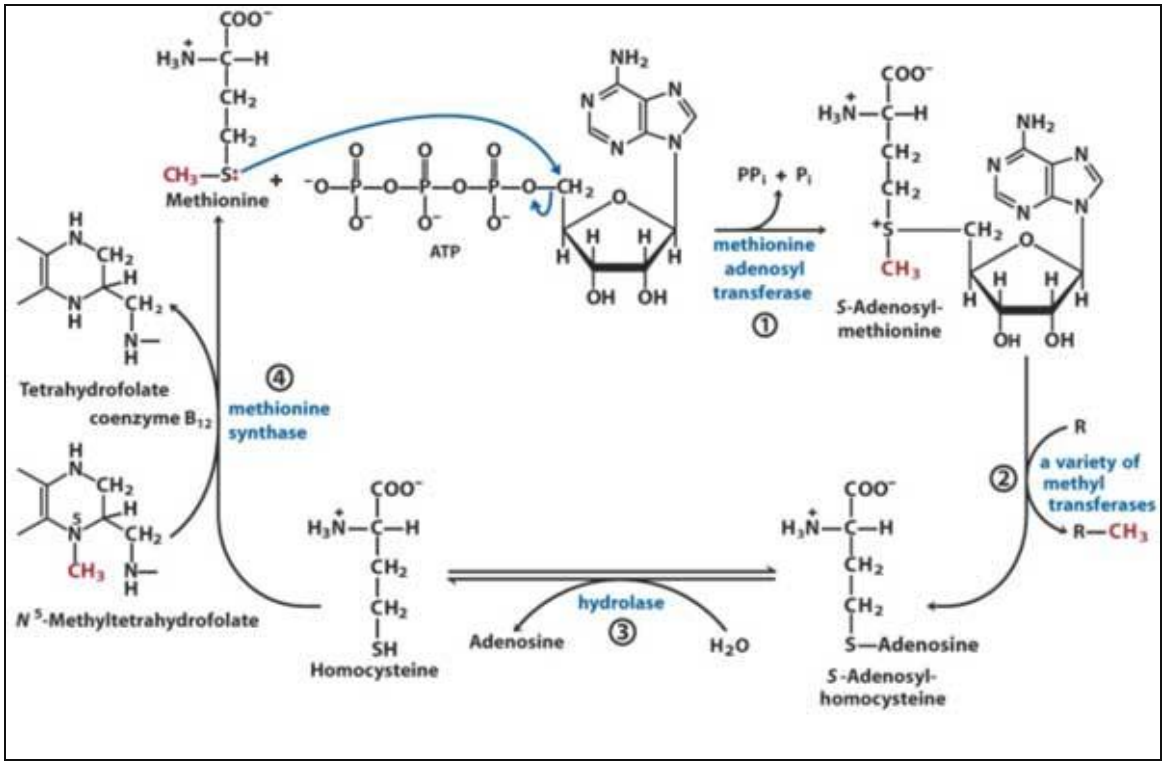
Where our Sex Drive comes from. TIME magazine; January 19, 2004

http://www.time.com/time/2004/sex/flash.html

Spermine & Spermidine, involved in DNA packaging, are also formed by Decarboxylation reactions.

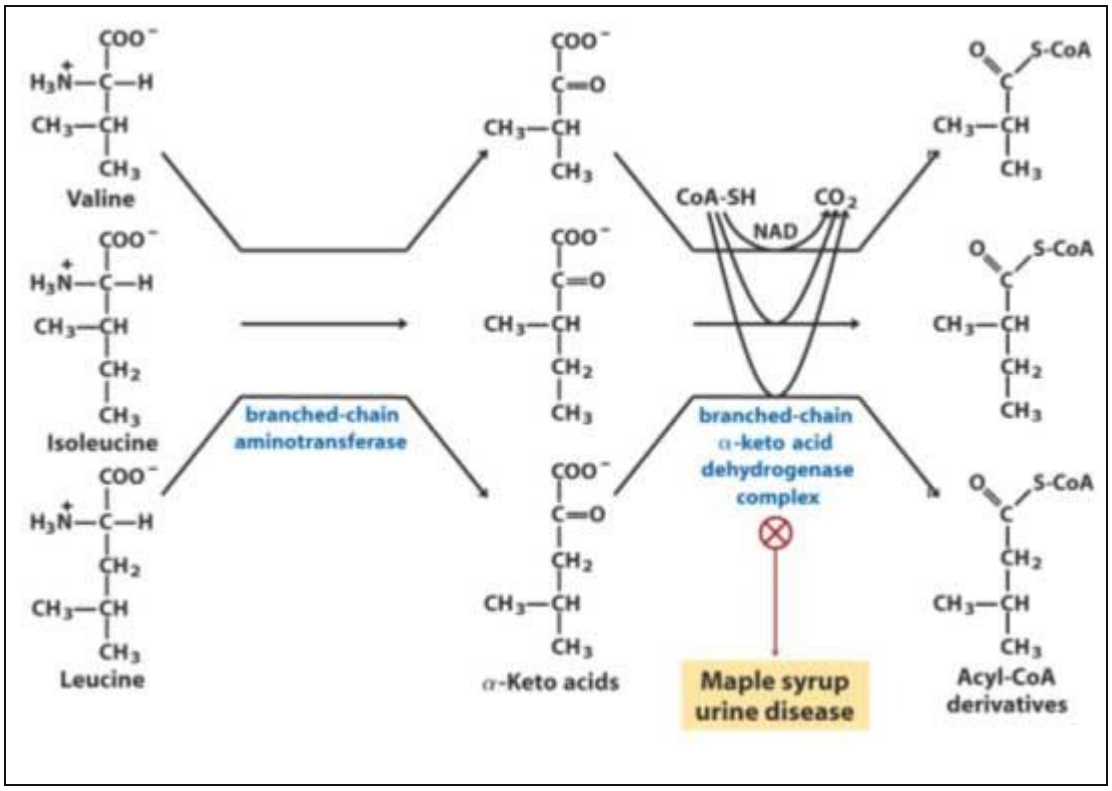


C. **Transmethylation.** Amino acids can also be metabolized by the transfer of methyl groups. An example would be the ultimate transfer of a **methyl** group from **methionine** to the methyl donor **S-Adenosylmethionine**. A variety of enzymes called **methyl transferases** will then transfer the methyl group to other molecules.

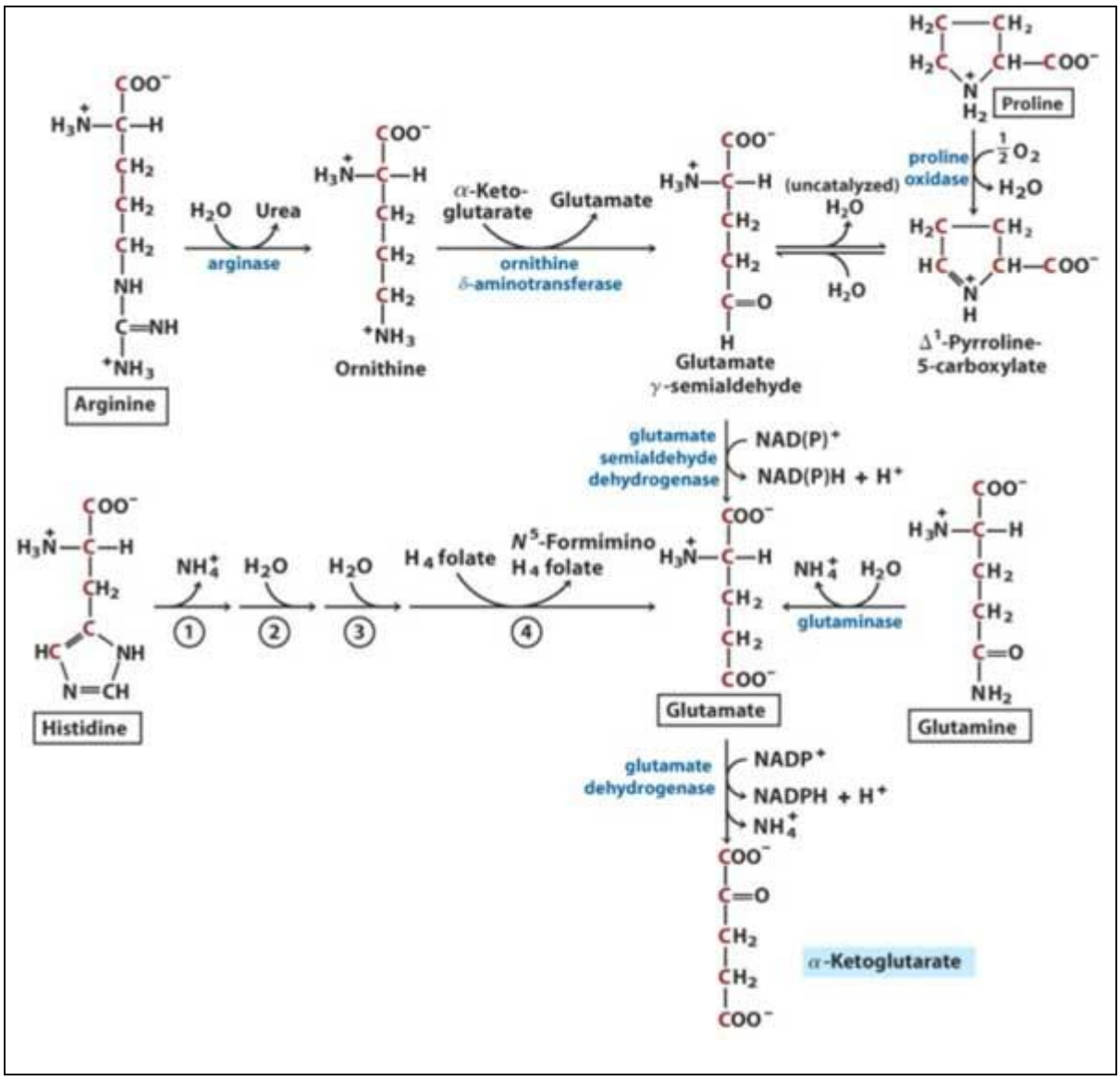


IV. SPECIFIC PATHWAYS FOR AMINO ACID CARBON METABOLISM

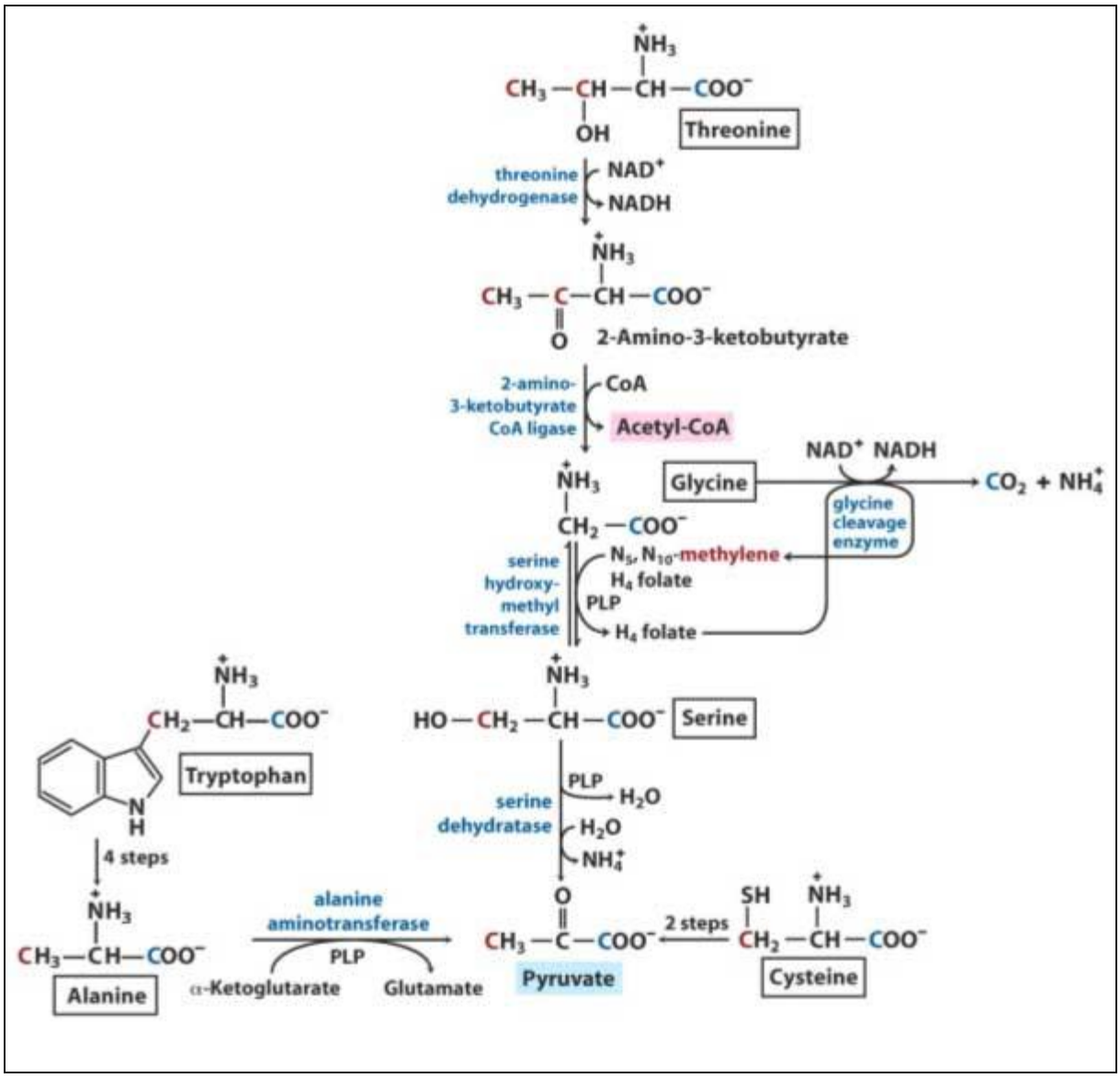
Branched Chain Amino Acids. Branched chain amino acids, Leucine, Isoleucine & Valine, are **not** degraded in the liver. They are oxidized as fuels primarily in muscle, adipose, kidney & brain tissue. These tissues contain an enzyme called **Branched-Chain Aminotransferase** converts these 3 amino acids to corresponding alpha keto acids. A defect in the **catabolism** of branched chain amino acids leads to the metabolic defect called **Maple syrup urine disease**.


Valine
Isoleucine
Leucine
branched-chain aminotransferase
α-Keto acids
CoA-SH
CO2
NAD
branched-chain α-keto acid dehydrogenase complex
Maple syrup urine disease
S-CoA
Acyl-CoA derivatives

Glutamate-Central Role. Throughout the various amino acid metabolic pathways, Glutamate has a central role as described earlier and shown here in.



Tryptophan The degradation of Tryptophan is the most complex of all the pathways of amino acid metabolism and can involve several multi-step processes. As discussed earlier, Tryptophan can also be converted to Serotonin.



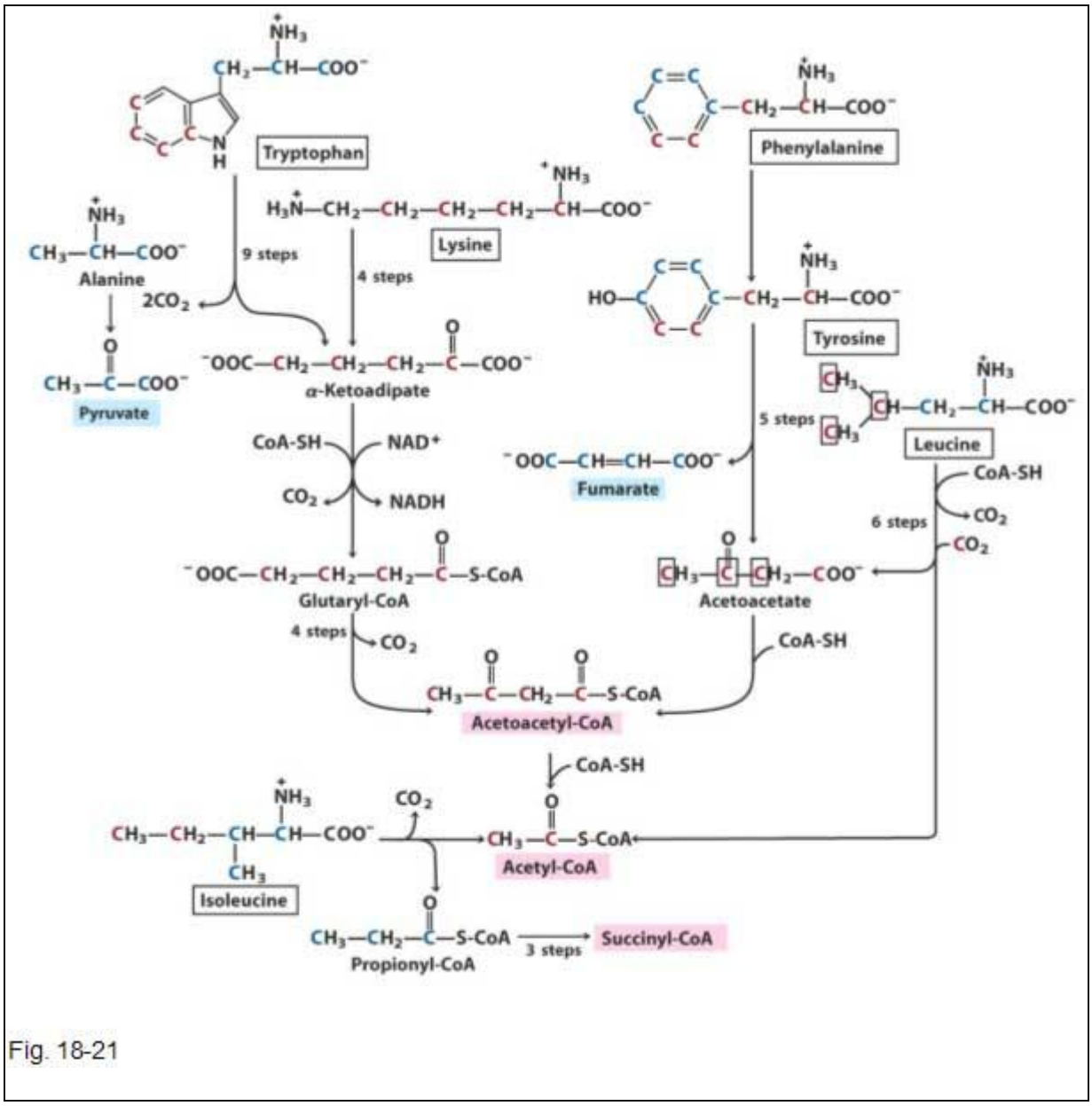
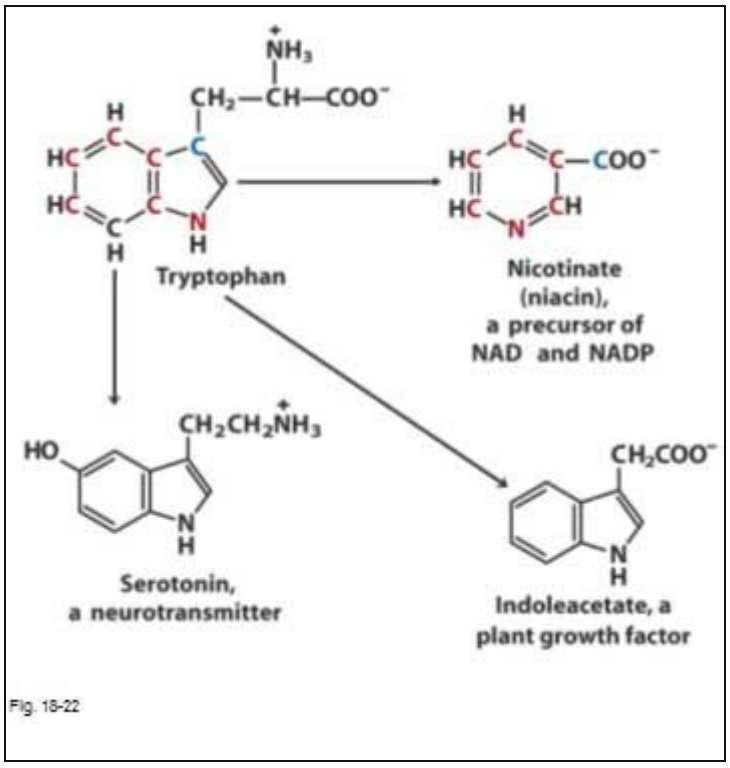
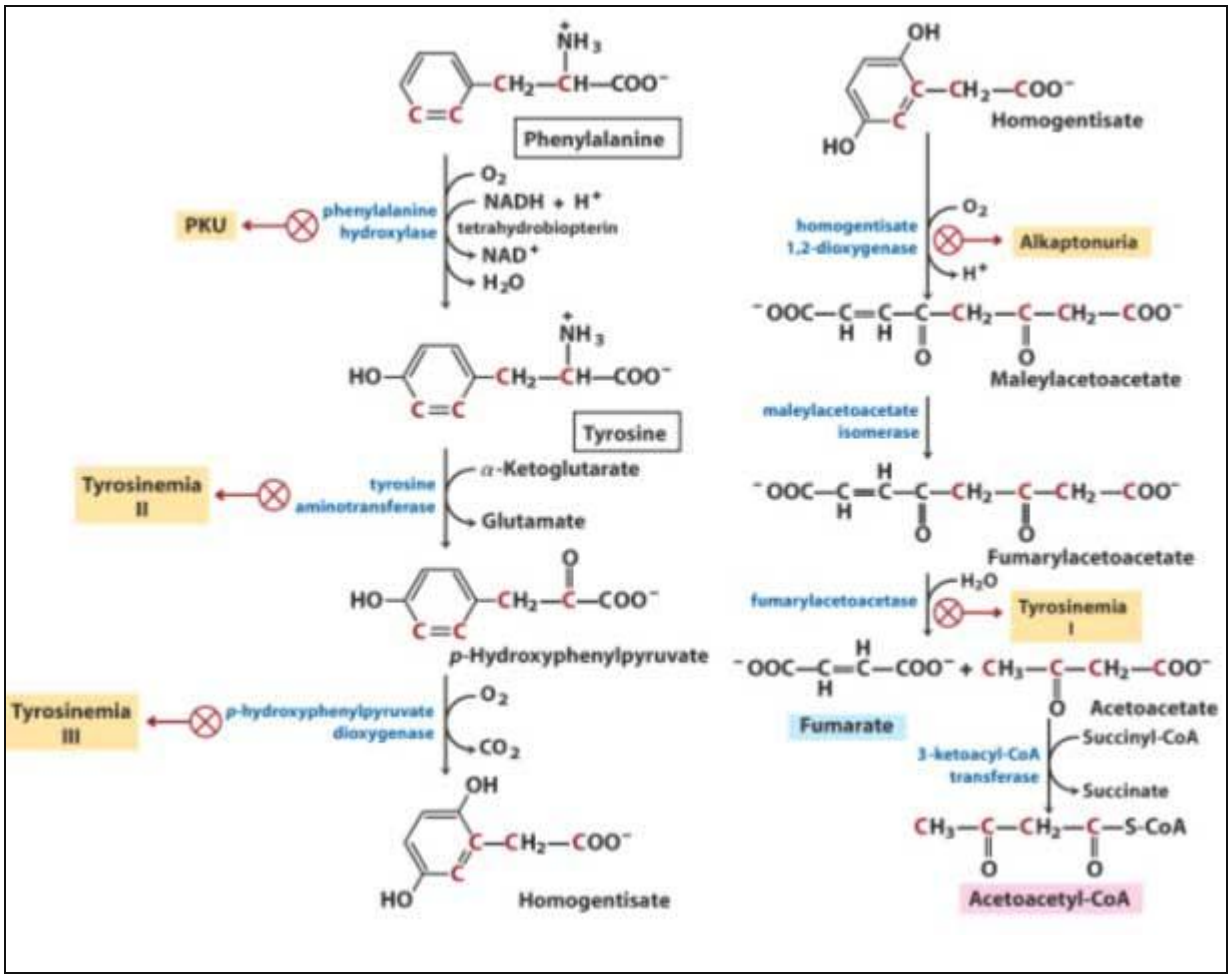

Tryptophan
Phenylalanine
Lysine
Alanine
9 steps
4 steps
2CO2
Pyruvate
α-Ketoadipate
Tyrosine
5 steps
Leucine
CoA-SH
NAD+
CO2
NADH
Fumarate
6 steps
CO2
Glutaryl-CoA
Acetoacetate
4 steps
CO2
CoA-SH
Acetoacetyl-CoA
CoA-SH
CO2
Isoleucine
Acetyl-CoA
Propionyl-CoA
3 steps
Succinyl-CoA

Fig. 18-21



Phenylalanine & Tyrosine

A. **Catabolism: Clinical Note**: A deficiency of **phenylalanine hydroxylase**, the enzyme required to convert Phenylalanine to Tyrosine, can lead to the pathologic condition known as **phenylketonuria PKU**. In the past a "diaper test" was used to detect this defect and the diet was adjusted to contain low phenylalanine to prevent mental retardation during the first 10 years. Now a "**neo natal**" screen is used. There are 8 to 10 cases per 100,000 births. Genetic defects in other enzymes in this pathway can cause several inheritable human diseases.



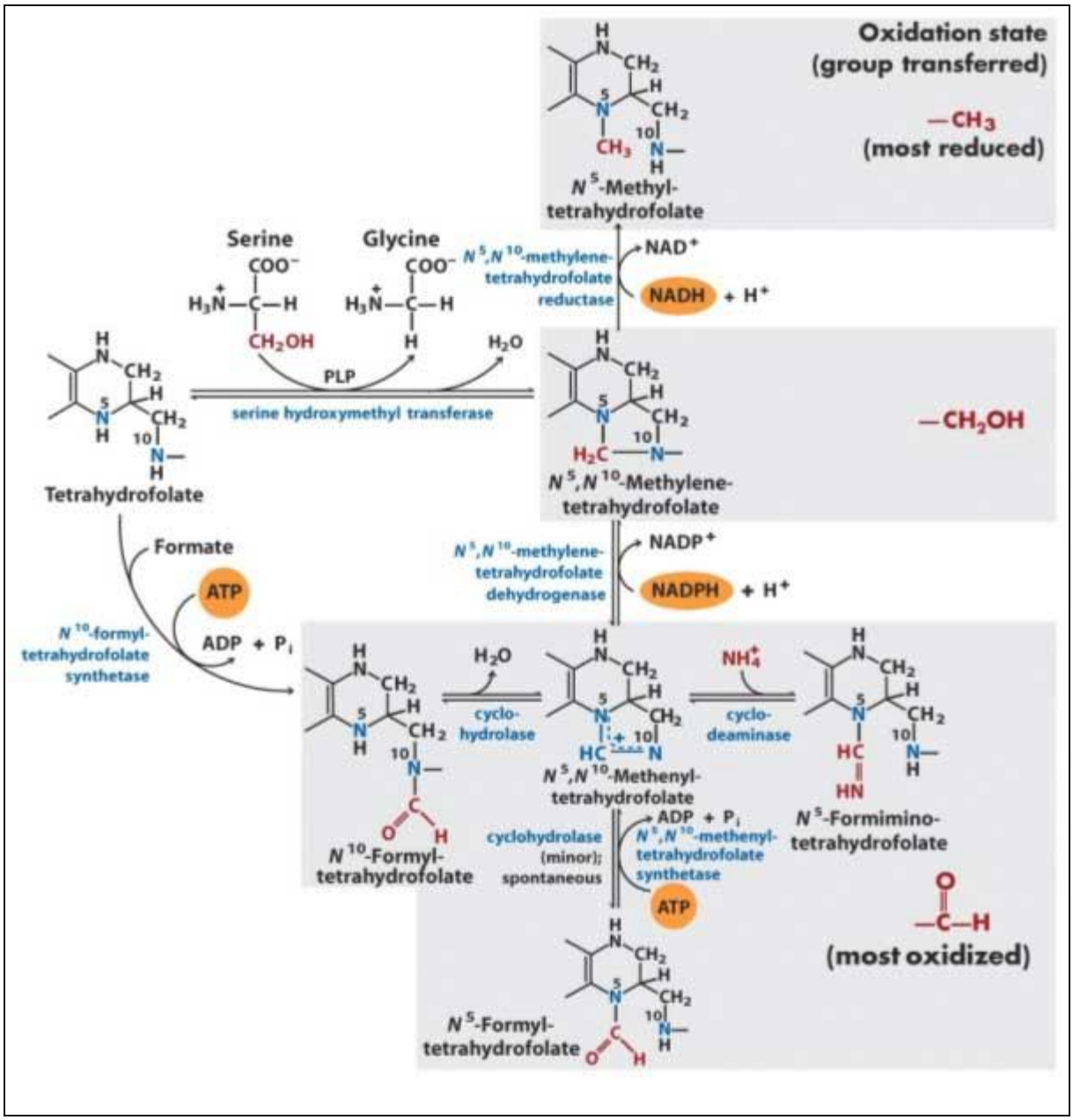
Dietary Sources of Phenylalanine
Cheeses
Nuts & seeds
Milk chocolate
Meat (excluding fat)
Poultry (excluding skin)
Fish & shellfish
Milk & Eggs
Aspartame (NutraSweet)

Clinical Note: Alkaptonuria: This is an inherited disorder that affects phenylalanine and tyrosine metabolism. This leads to excretion of **homogentistic acid** in the urine, which makes the **urine appear black**. Usually, the condition does not result in any serious ill effects.

Phenylalanine, after it is hydroxylated to yield Tyrosine, can also provide the precursor of the catecholamines **Epinephrine** and **Norepinephrine** secreted by the adrenal gland. Phenylalanine and tyrosine can also supply structures to form the neurotransmitter **dopamine** and **melanin**, the black pigment of skin & hair.

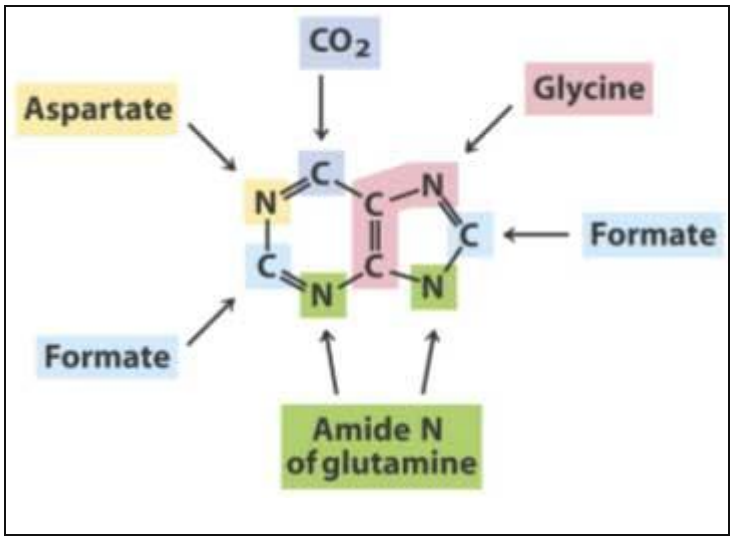
V. ONE CARBON METABOLISM

A. Tetrahydrofolate is a key co-factor in many metabolic pathways involving the amino acids. It can exist in several oxidation states and is able to mediate the transfer of methyl groups.



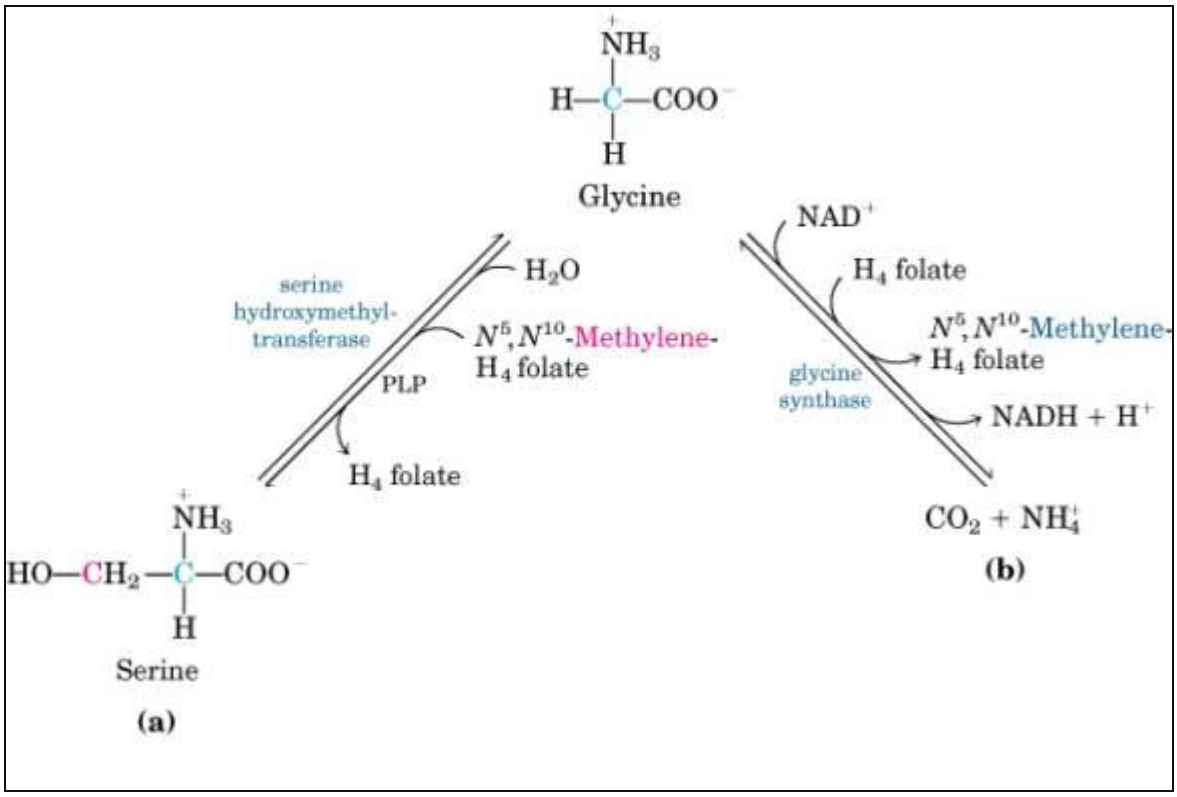
Sources of Tetrahydrofolate: Dietary sources (meats & green veggies) provide **folic acid** that is reduced to Dihydrofolate and then to Tetrahydrofolate by Dihydrofolate reductase.

N^{10}-Tetrahydrofolate is the precursor of **FORMATE** that contributes 1 Carbon units to the ring structure of the Purines.

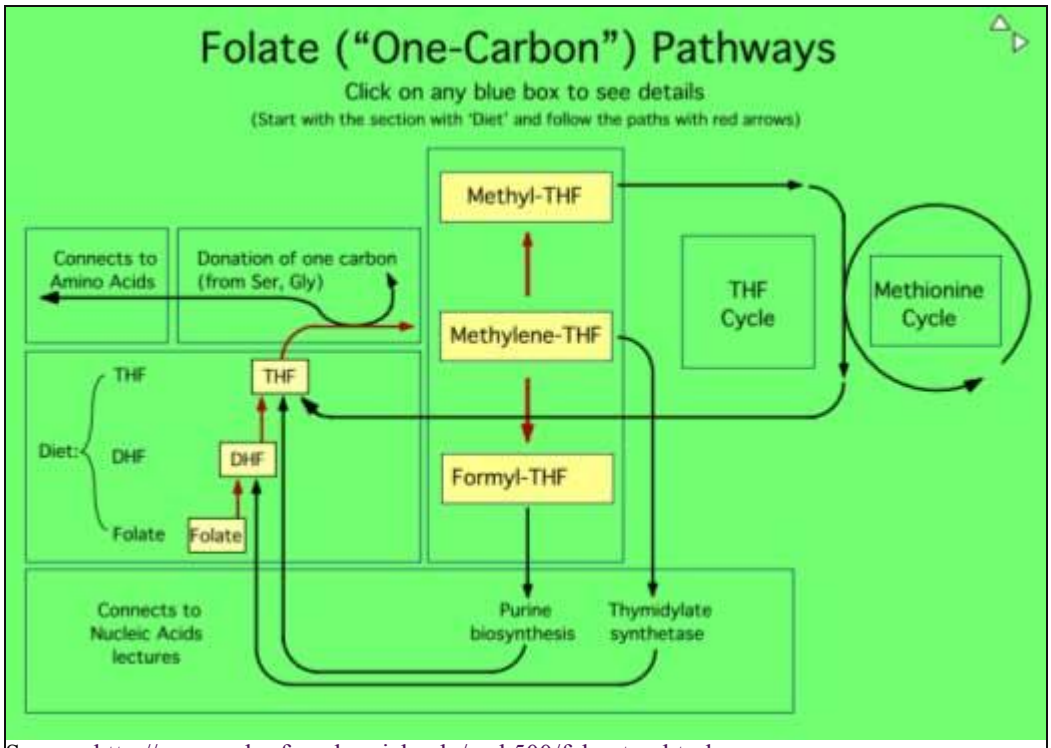


Clinical Note: There are several pathologies associated with folate deficiency. The symptoms include weakness, anemia and anorexia. There is also the appearance of large, immature erythrocytes (megaloblasts) in the blood. Alcoholism may compound folate deficiency. Folic acid is also needed to reduce the level of homocysteine in the blood. Homocysteine is an amino acid in the blood and excessive levels of it are related to a higher risk of coronary heart disease, stroke and peripheral vascular disease. Women at increased risk for **spina bifida** should take 4000 micrograms (mcg) of folic acid by prescription for 1 to 3 months before becoming pregnant. Source: Spina Bifida Association of America

Serine can be metabolized to Glycine by giving up its one carbon methyl group to Tetrahydrofolate. Subsequently, Glycine can be metabolized back to Serine or broken down to carbon dioxide and ammonia.



Summary of Folate One Carbon Pathways



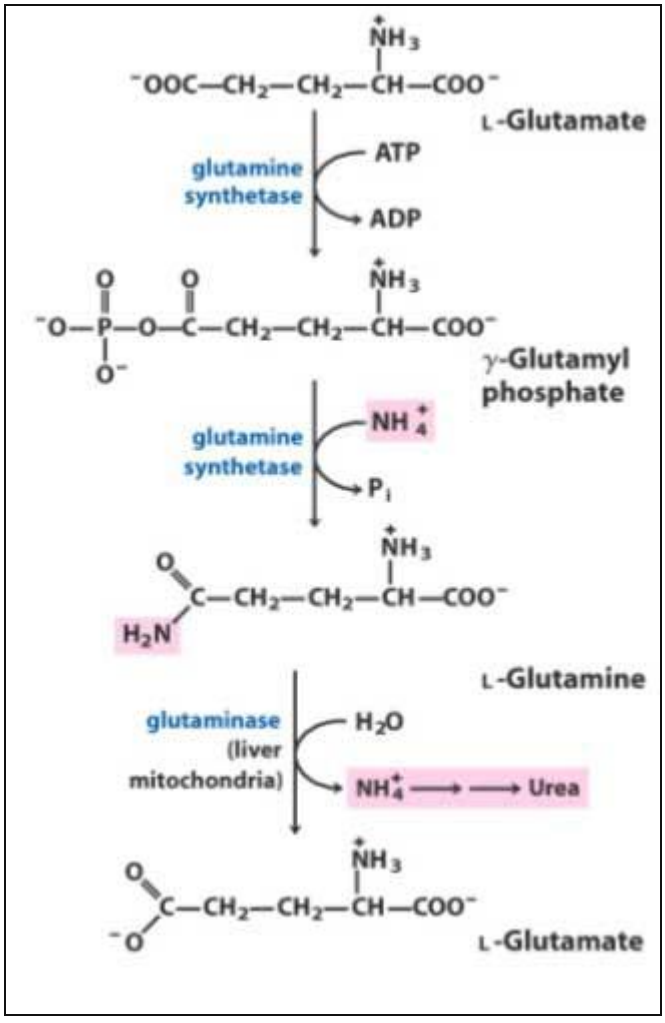
Source: http://seqcore.brcf.med.umich.edu/mcb500/folmetov.html

As described above under the topic "**Transmethylation**", S-Adenosylmethionine (SAM) is a biological methylator and is an important mediator in the formation of several bio-active amines. SAM participates in the conversion of Norepinephrine to Epinephrine. SAM also transfers Methyl groups during the process of mRNA and DNA methylation.

VI. METABOLIC PROCESSING OF AMINO ACID NITROGEN

A. Transport of Metabolic Nitrogen from Periphery to Liver

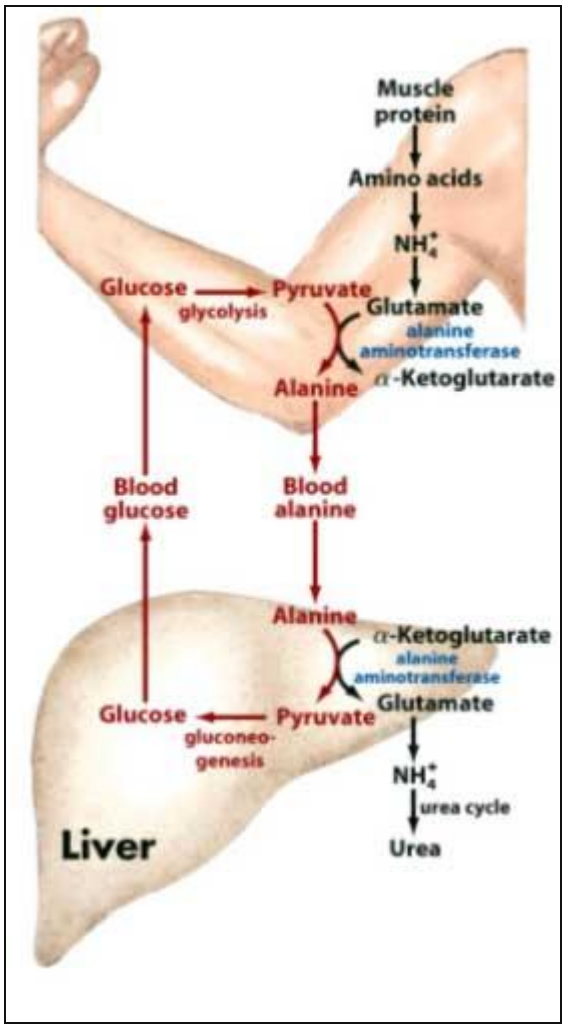
1. Glutamine. Ammonia itself cannot be transported to the liver for further metabolic processing. Therefore it is incorporated into Glutamate by the enzyme **Glutamine Synthetase** to form the non-toxic amino acid **Glutamine**. This enzyme converts Glutamate to Glutamine in a 2 stage reaction and requires **ATP**.



Glutamine is a neutral, non-toxic compound and can readily pass through cell membranes whereas Glutamate cannot. Glutamine is then carried by the blood to the liver where in the mitochondria of the hepatocyte, the amide nitrogen is released as ammonia when the enzyme Glutaminase converts the Glutamine back into Glutamate.

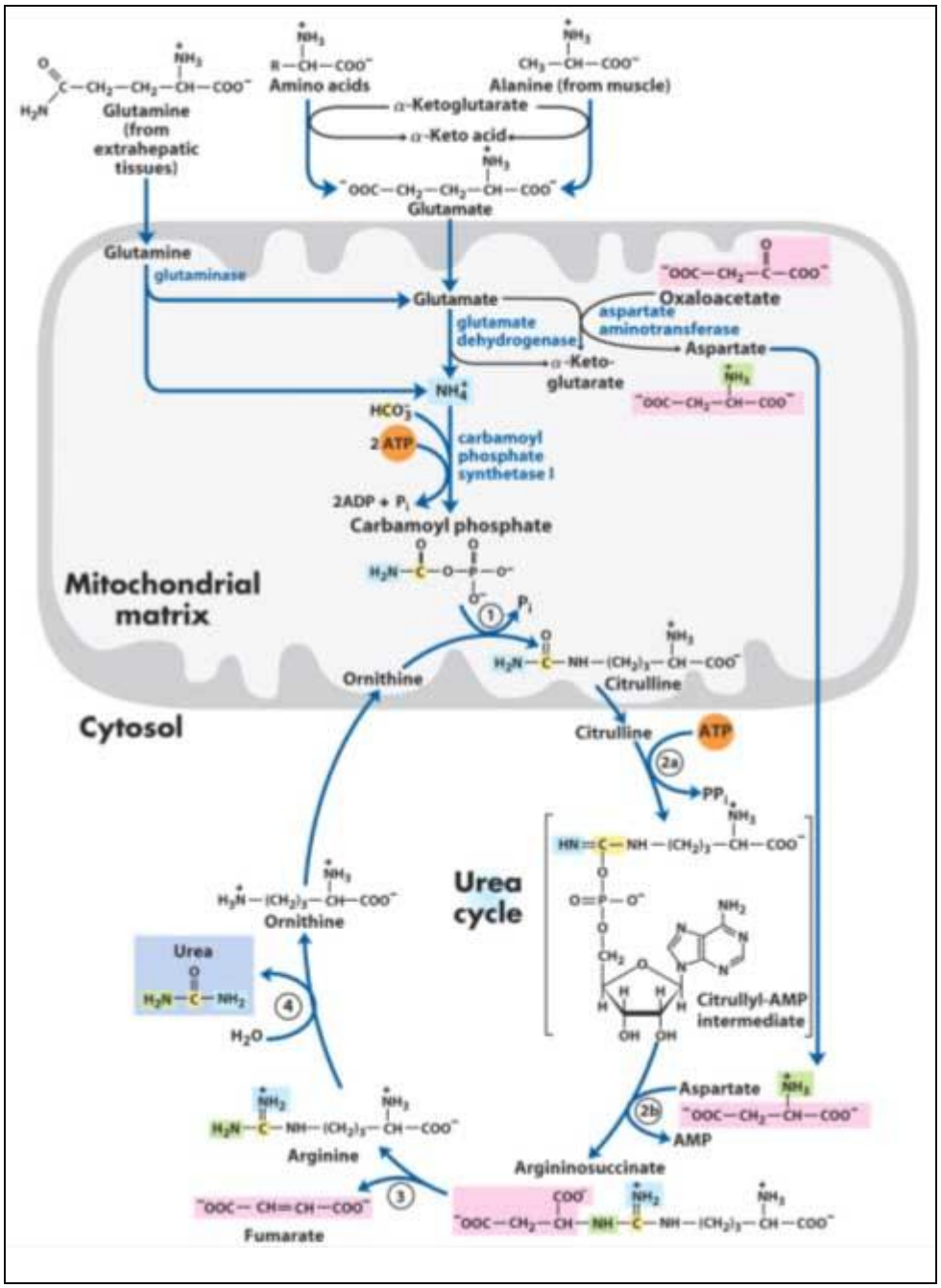
Alanine Cycle. Another important pathway to transport ammonia groups to the liver from peripheral tissues is the **Alanine cycle**. Excess ammonia is incorporated into Glutamate and then transferred to **pyruvate** by the action of the enzyme **Alanine aminotransferase** to form **Alanine**. The Alanine, with no net charge at pH near 7,

readily passes into the blood where it is transported to the liver. In a reversal of the reaction that took place in the muscle, Alanine is converted back to pyruvate and the ammonia is transferred back to glutamate where it is metabolized in the mitochondria to eventually be released as urea.



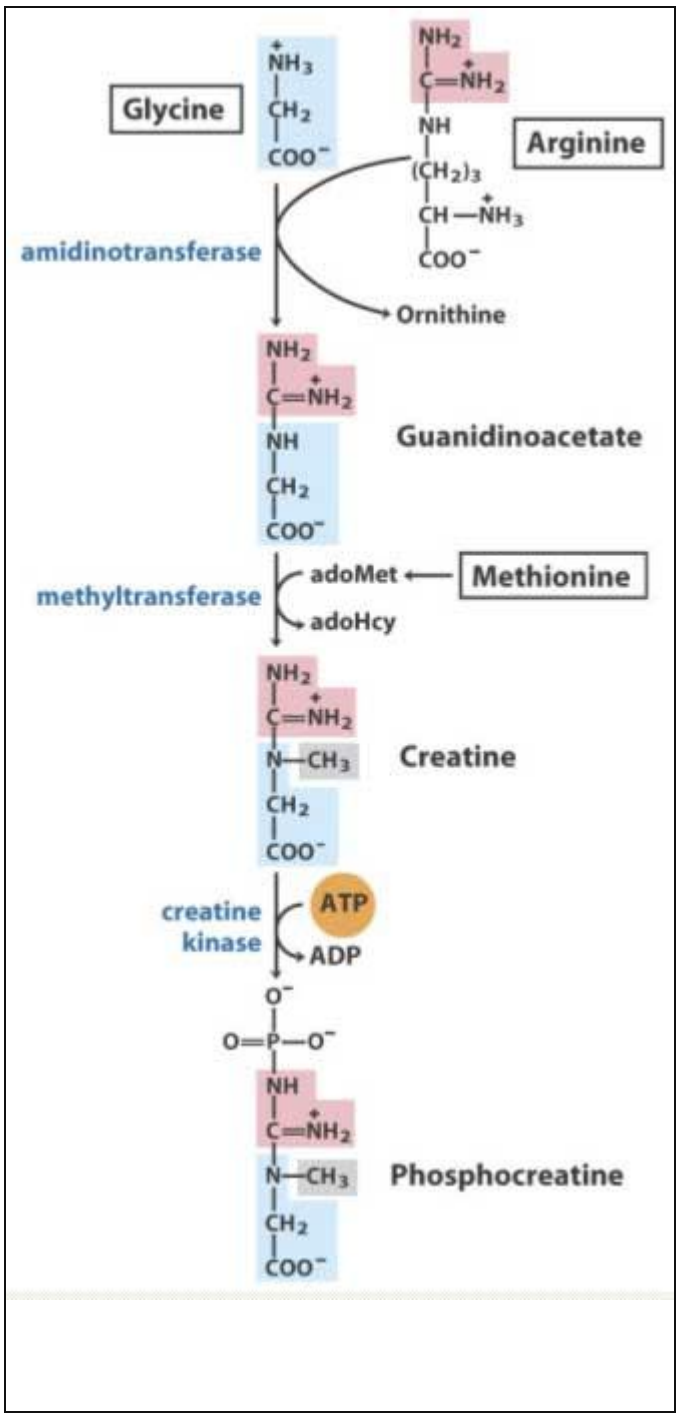
VII. THE UREA CYCLE

First of all note that the reactions involved in the Urea Cycle are distributed between the liver mitochondria & the cytosol. One amino group enters the cycle from Carbamoyl phosphate. This reaction consumes 2 ATP molecules. The other amino group is formed from Aspartate also generated in the mitochondria. Aspartate donates a nitrogen atom **directly** for the formation of urea. In the actual cycle, Citrulline is formed from Ornithine in the mitochondria. Next, Citrulline combines with Aspartate to form the complex called Argininosuccinate. This reaction consumes the 3rd ATP. Next, Arginine is generated with the release of Fumarate. This Fumarate then enters the Citric Acid Cycle. The Arginine then reacts with water releasing its amino group forming Urea that is then excreted. Ornithine is regenerated to start the cycle over again. **Note**: 3 ATP molecules are required for the production of 1 molecule of urea.



1. Cycle begins in the liver mitochondria
2. Urea produced in the cytosol
3. 3 ATPs required for 1 molecule of Urea
4. Asparate donates a Nitrogen **directly** to Urea

Creatine is the precursor of Phosphocreatine; an important energy reservoir in skeletal muscle and it is derived from Glycine, Arginine and Methionine.



Genetic Disorders Affecting Amino Catabolism

DO NOT MEMORIZE

TABLE 18-2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

Medical condition	*Approximate incidence (per 100,000 births)*	*Defective process*	*Defective enzyme*	*Symptoms and effects*
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation: white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

NOTE: YOU ARE NOT RESPONSIBLE FOR DETAILED CHEMICAL STRUCTURES OR COMPLETE CHEMICAL REACTIONS. HOWEVER, YOU SHOULD KNOW EXAMPLES OF HOW SPECIFIC ENZYMES ARE IMPORTANT IN AMINO ACID METABOLISM AND GENETIC DISEASES.

UNDERSTAND THE "BIG PICTURE" !!!!!!!!

Major Concepts to be understood

1. Dietary proteins are the primary source of biologically useful nitrogen in our bodies.
2. The general scheme for the further metabolism of "digested" amino acids involves the transfer of the amino group to alpha-ketoglutarate forming glutamate plus an alpha-keto acid.
3. The glutamate produced is transported to liver mitochondria and deaminated by glutamate dehydrogenase.
4. Glutamine and alanine transport ammonia formed in other tissues to the liver.
5. Nitrogen is excreted as ammonia or urea. High serum levels of ammonia could indicate liver disease.

6. Urea is formed from ammonia in a series of reactions called the urea cycle.
7. Deaminated amino acids produce carbon skeletons that can be funneled into the citric acid cycle.
8. Amino acids can serve as important sources of energy.
9. Amino acids serve as precursors for very important biological amines.
10. Some amino acids are ketogenic, some are glucogenic and some are both. Ketogenic amino acids are degraded to acetoacetyl-CoA and/or acetyl-CoA that can be converted to ketone bodies.

Glucogenic	**Ketogenic**	**Both**
Glycine	Leucine	Threonine
Serine	Lysine	Isoleucine
Valine		Phenylalanine
Histidine		Tyrosine
Arginine		Tryptophan
Cysteine		
Proline		
Hydroxyproline		
Alanine		
Glutamate		
Glutamine		
Asparate, Asparagine, Methionine		