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carbohydratesisomersketone starchlipidproteinamine

Biochemistry 2

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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Introduction

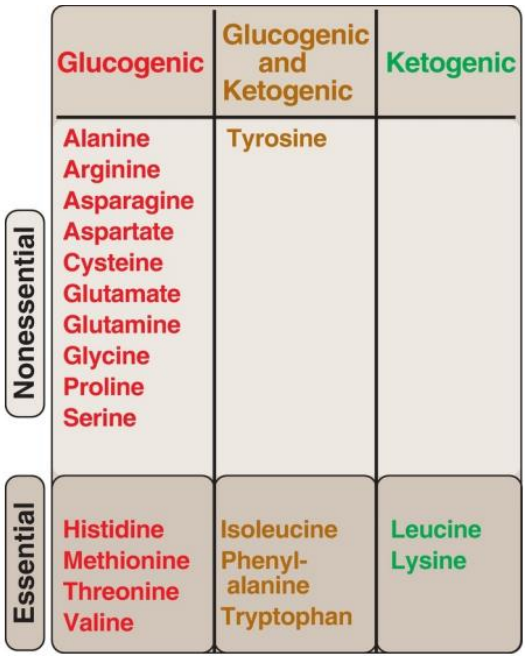
As discussed previously, amino acids are not stored in our body. Therefore, any extra amino acids that remain (some may have been used for synthesis of proteins or other nitrogenous compounds) need to be degraded. This degradation began with removal of the alpha-amino group through transamination and then oxidative deamination. The result was the release of free ammonia, which is toxic and dealt with through the Urea Cycle. What remains of the amino acid is the carbon skeleton, which contains the R group. The focus of this sheet is to see the catabolic pathways these carbon skeletons can undergo. These pathways will differ between amino acids because their R groups differ.

The pathways by which amino acids are catabolized are organized according to which one (or more) of the seven intermediates is produced from a particular amino acid. These intermediate products are:

Oxaloacetate **Fumarate**	**Pyruvate** **Succinyl CoA** **Acetoacetate**	**α-ketoglutarate** **Acetyl CoA**

These products can then be used for other purposes, and amino acids can be classified based on this:

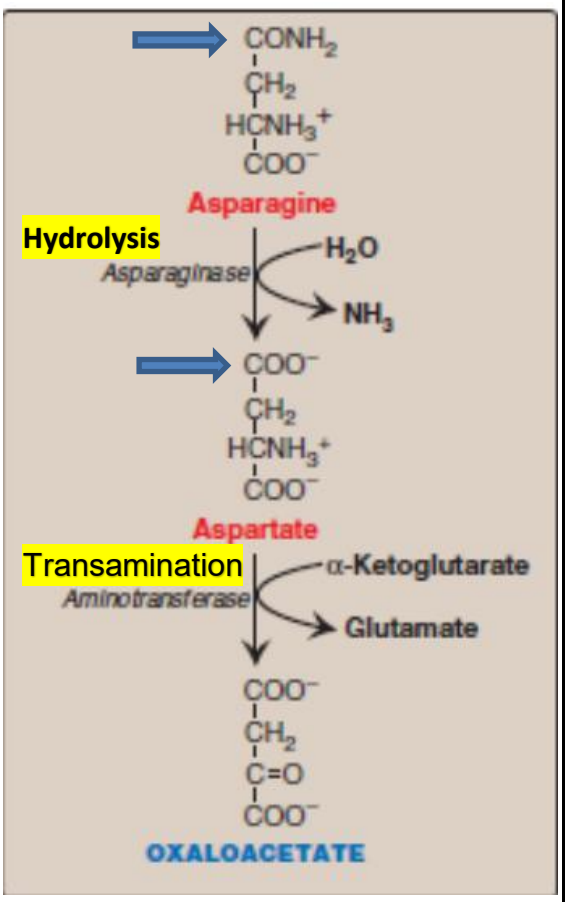
1. **Glucogenic amino acids** yield pyruvate or one of the TCA cycle intermediates (Krebs) that can be used as substrates for **gluconeogenesis** in the liver and kidney.
2. **Ketogenic amino acids** can be used to produce **ketone bodies**.
   They yield either acetoacetate (a type of ketone body) or one of its precursors acetyl CoA or acetoacetyl CoA.
   - Other ketone bodies are 3-hydroxybutyrate and acetone.



- The majority of amino acids, whether essential or nonessential are gluconeogenic.
- The ketogenic amino acids are Leucine and Lysine (both start with the letter "L")
- Amino acids can be both gluconeogenic and ketogenic. They are Isoleucine and the aromatic amino acids with a benzene ring in their side chain.

As can be seen, the degradation processes of amino acids are also connected to synthesis. While the amino acid and its carbon skeleton are being broken down, other products are being synthesized. Next, we will discuss each product and the amino acids that can synthesize it.

a) Amino Acids That Form Oxaloacetate



1. Aspartate

- *Reaction* - Aspartate undergoes a **transamination** reaction to become oxaloacetate. The amino group is removed from aspartate and given to α-ketoglutarate to form glutamate. What remains is oxaloacetate, the α-ketoacid of aspartate.
- *Enzyme* – Aspartate Aminotransferase (AST)

2. Asparagine

- *Structure*- Asparagine is similar in structure to Aspartate. The difference is that aspartate has a carboxyl group while asparagine has an amide group in its side chain. (see blue arrows)
- *Reactions* – The conversion of asparagine into oxaloacetate is a **two step** process. The first is **deamination** of asparagine in a **hydrolysis** reaction to form aspartate. This is catalyzed by **asparaginase**. Then, aspartate is converted into oxaloacetate.

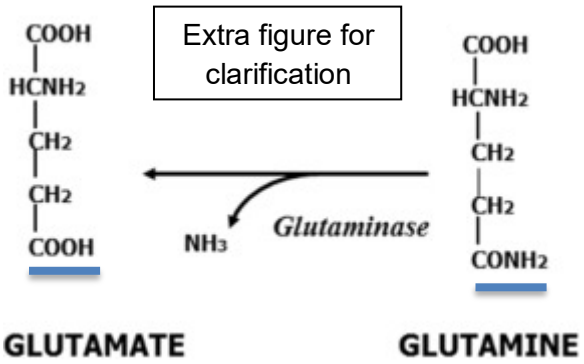
b) Amino Acids That Form α-ketoglutarate Via Glutamate

* They must first be converted into glutamate and then converted into α-ketoglutarate.

1. Glutamine

The idea here is the same before with asparagine and aspartate. A similar two step reaction occurs:

1. Glutamine is converted to glutamate and ammonia by the enzyme **glutaminase**.
2. Glutamate is converted to α-ketoglutarate by transamination *or* through oxidative deamination by **glutamate dehydrogenase**.



2. Proline

Proline is oxidized to glutamate. This conversion occurs through the opening of the ring structure and reorganization of the groups.

3. Arginine

Arginine is cleaved by arginase to produce Ornithine in the liver as a part of the urea cycle. Then ornithine is converted into glutamate which is converted into α-ketoglutarate.

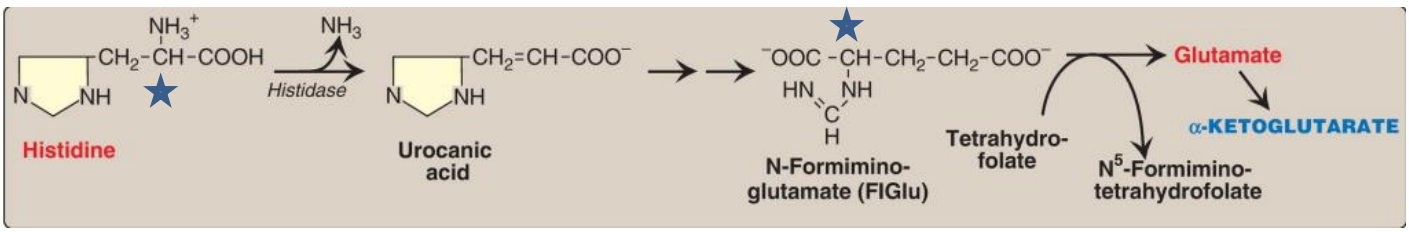
4. Histidine

- *Structure* - Histidine has an imidazole ring.
- *Reactions*
  1. Histidase removes an amino group from the alpha carbon (NOT the side chain as seen with asparagine and glutamine). This oxidative deamination forms urocanic acid.
  2. A series of steps is undergone to open the ring structure, so a chain is what remains. The placement of the alpha carbon has changed (the stars in the figure below refer to where the alpha carbon is). This structure is now glutamate with a group attached to the amino group. This group (HC double bond NH) is known as a **formimino group**. So, the name of the compound is N-Formimino-Glutamate (FIGlu).
  3. The formimino group is removed to give glutamate. This is done with the help of **tetrahydrofolate (THF),** which can carry single carbon units (such as formimino).
  4. Glutamate dehydrogenase converts glutamate into α-ketoglutarate.

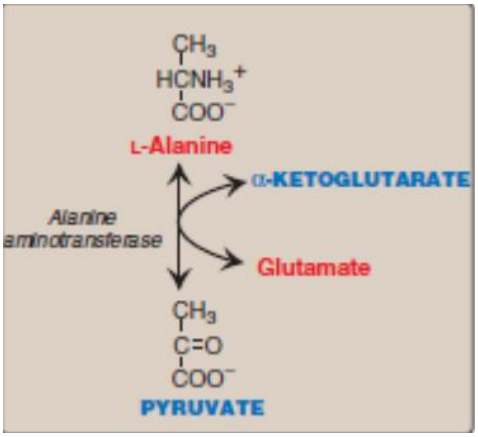
A formyl group is HC double bond O. Since here it is HC double bond N (HC=N), the name is changed to formimino.

Tetrahydrofolate is the active form of vitamin B9 (folic acid)

- *Folic Acid Deficiency* – If folic acid is deficient, then THF is deficient. Therefore, individuals deficient in folic acid excrete high amounts of FIGlu in the urine (as it can not be converted into glutamate). That's why an FIGlu excretion test can be used in diagnosing folic acid deficiency.



c) Amino Acids that Form Pyruvate



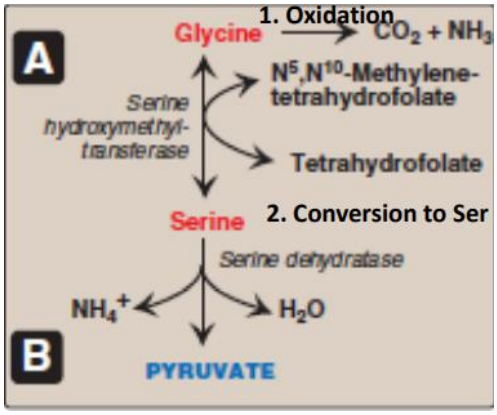
1. Alanine

Alanine loses its amino group by transamination to form pyruvate, its α-ketoacid. This is catalyzed by alanine aminotransferase (ALT).

2. Serine

Serine has an OH group (side chain) and an amino group (backbone) that is not found in pyruvate and therefore must be removed. **Serine dehydratase** catalyzes the reaction in which H_2O and NH_4^+ are removed and pyruvate is formed.

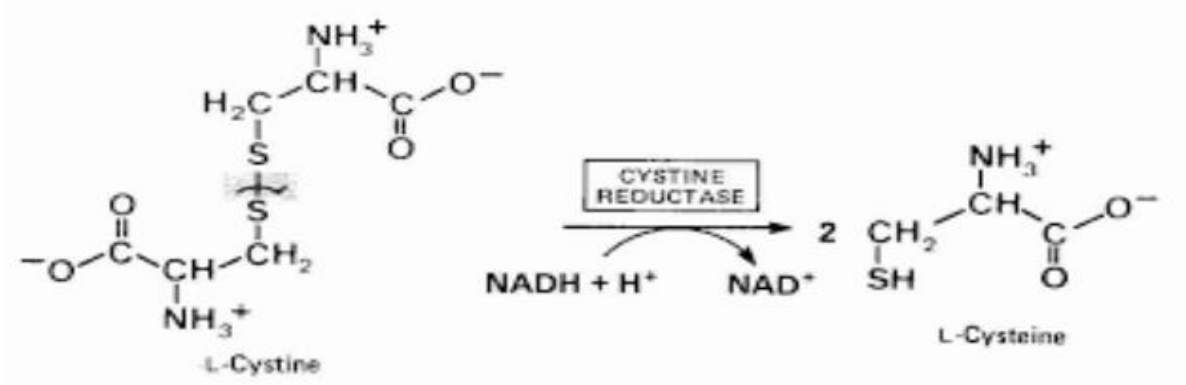
3. Glycine



- *Structure:* Glycine is very simple, and only has a hydrogen in its side chain.
- *Conversion to Pyruvate:*
  1. Glycine is first converted to Serine. To do so, it needs a carbon-OH group added. The enzyme that catalyzes this reaction is **serine hydroxymethyl-transferase** (the name indicates the group that is being added). This single carbon unit is brought by N^5,N^{10}-Methylene-tetrahydrofolate.
  2. Serine is converted to Pyruvate.
- *Another Possible Reaction:*
  - As a simpler molecule glycine has another metabolic pathway. Oxidation of glycine gives NH_3 and CO_2.
  - This occurs through conversion of glycine to glyoxylate (through deamination), which is then oxidized to oxalate. Or, glyoxylate can be transaminated back to glycine.
  - Deficiency of the transaminase causes overproduction of oxalate and kidney damage (primary oxaluria Type 1).

4. Cysteine

- *Structure* – Cysteine has a thiol group (SH). This is similar to serine, except serine has a hydroxyl group (OH). Consequently, the conversion to pyruvate will be similar.
- *What if it starts as Cystine?* – (refer to the figure in the next page) Cystine is the oxidized dimer form of cysteine. It must be reduced to cysteine, with NADH and H^+ acting as reductants. Then cysteine can be converted to pyruvate.
- *Reaction:* Cysteine desulfuration with removal of the amino group yields pyruvate.



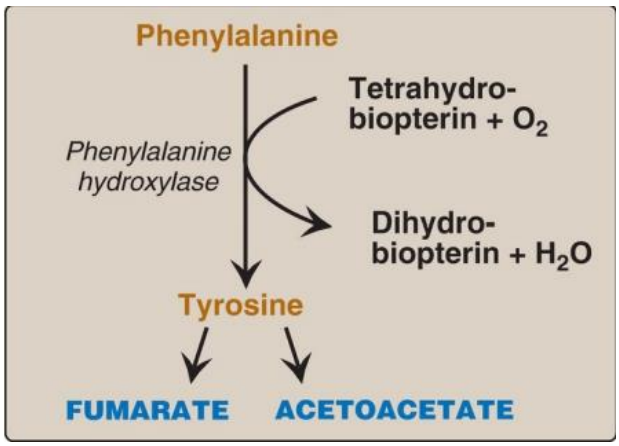
5. Threonine

- *Structure* – Threonine is similar in structure to Serine, but it has an additional carbon in its side chain.
- *Possible Reactions*:
  1. Threonine can be converted to pyruvate in a reaction similar to that of serine's.
  2. Threonine can also be converted to α-ketobutyrate, which forms succinyl CoA.

d) Amino Acids That Form Fumarate

1. Tyrosine

- *Structure* – Has a benzene ring with an OH group (phenol)
- *Metabolic Pathways*
  1. Glucogenic – Tyrosine is converted into fumarate
  2. Ketogenic – Tyrosine is converted into acetoacetate



2. Phenylalanine

- *Structure* – Has a benzene ring
- *Reaction* – Phenylalanine is hydroxylated to tyrosine by the enzyme **phenylalanine hydroxylase**. Then tyrosine is converted to acetoacetate or fumarate.
  - ❖ As can be seen, phenylalanine and tyrosine are both glucogenic and ketogenic.
  - ❖ Inherited deficiencies in the enzymes that metabolize phenylalanine and tyrosine lead to phenylketonuria, alkaptonuria and albinism.

e) Amino Acids That Form Succinyl CoA

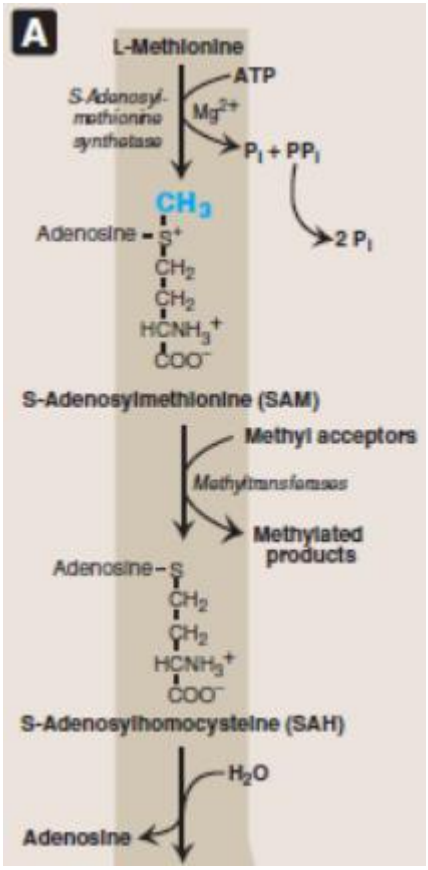
1. **Valine and isoleucine** are branched-chain amino acids. They generate propionyl CoA that is converted to succinyl CoA by biotin and vitamin B12– requiring reactions.

2. Threonine

Threonine is dehydrated to α-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA. It can also form pyruvate as previously mentioned.

3. Methionine

- *Importance* - In protein synthesis it is always the first amino acid, whether it's included in the final protein or it's cleaved. It can also be converted to S-adenosyl methionine (SAM), the major methyl-group donor in one-carbon metabolism. SAM is similar to THF, except SAM only gives CH_3, while THF can give multiple single carbon units.
- *Structure* - Methionine has sulfur placed in between two carbons.
- *Reactions*



1. Synthesis of SAM – Metabolism of methionine starts with adding adenosine (a nucleoside) to methionine at the sulfur atom, forming SAM. SAM is a high energy compound (that has no phosphate) and this reaction requires ATP. The enzyme is S-Adenosyl-Methionine Synthetase.
2. Sulfur, with three bonds, now has a positive charge. So, SAM can easily donate the methyl group to methyl acceptors with the help of methyltransferases. This forms methylated products. What remains of SAM is S-Adenosylhomocysteine (SAH)
   - An example of an acceptor molecule is norepinephrine which leads to the synthesis of epinephrine.
   - The methyl group is transferred to O, N, or C atoms.
   - Methyl transfer is irreversible because of free energy loss.
3. SAH is hydrolyzed to homocysteine and adenosine.
4. This is where the metabolic pathway branches. There are two possible fates for homocysteine:
   a) <u>Transulfuration pathway if methionine is available to be converted to cysteine</u>
      i. Homocysteine is converted to cystathione. Reaction catalyzed by **cystathione β-synthase**, with **vitamin B6** as a cofactor. Serine is added and an H_2O molecule is removed.

Homocysteine is called so because it resembles cysteine. It has an SH group at the end of its chain.

ii. Cystathionine is converted into Cysteine. This is catalyzed by **γ-Cystathionase**, with **vitamin B6**. Here, water is added. Additional end products are **α-ketobutyrate** and NH_4^+. Enzyme called a "thionase" as it degrades cystathionine.

iii. The resulting α-ketobutyrate is oxidatively decarboxylated to form propionyl CoA that is then converted to **succinyl CoA.**

iv. Here the degradation of methionine (an essential AA) led to the synthesis of cysteine (a nonessential amino acid)

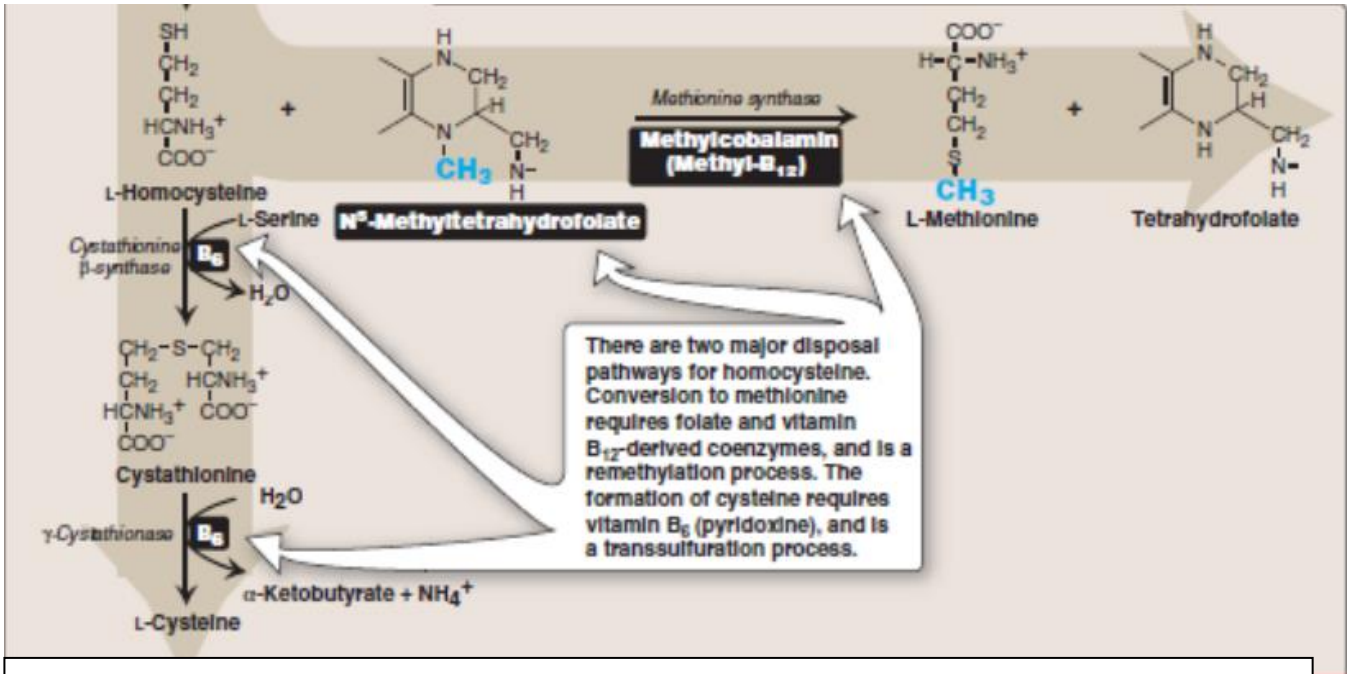
b) <u>Remethylation if Methionine is deficient</u>

i. **Methionine synthase** works with the coenzymes **B12 and N^5-Methyltetrahydrofolate** (serves as a methyl donor to return the methyl that was lost).

ii. Vitamin B12 can not work as a coenzyme here without tetrahydrofolate, but tetrahydrofolate can work without B12.

iii. If someone has B12 or folic acid deficiency, this reaction can't occur. This leads to the accumulation of homocysteine, which leads to increased production of cysteine.

<u>What enzymes are activated and what coenzymes are available determine which of these two pathways is followed.</u>



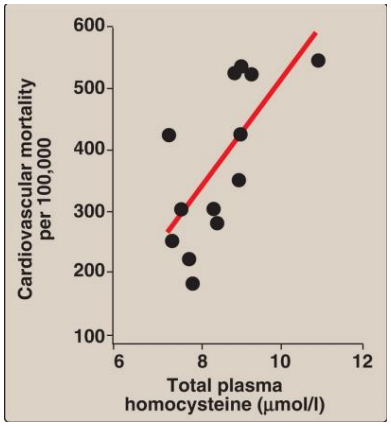
Why is methionine an essential amino acid if it's synthesized here?

It's because methionine is still needed from the diet in the first place to form homocysteine.

Then why synthesize methionine from methionine?

The purpose of this pathway is to produce SAM as methyl donors are limited (there's only SAM and tetrahydrofolate) and there are many methylation reactions in the body. And, again, methionine is an important amino acid.

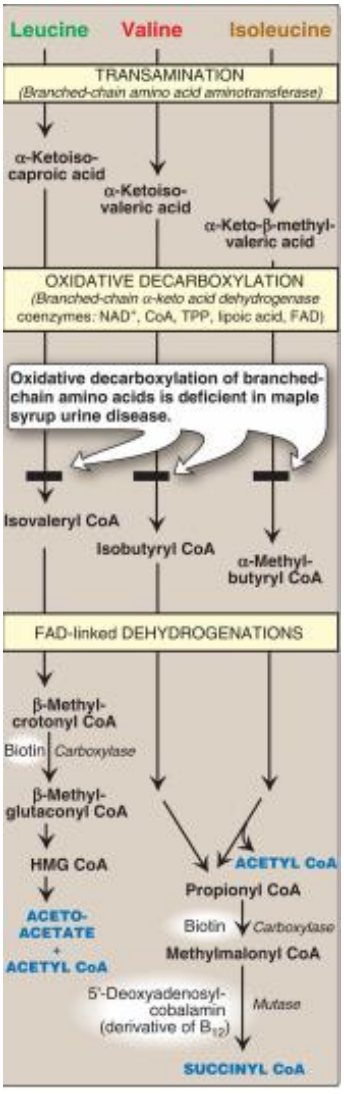
Clinical Hint: Homocysteine and Vascular Disease



- It is important to not allow homocysteine to accumulate as it is related to many diseases, especially cardiovascular diseases.
- High homocysteine levels promotes oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease
- Homocysteine levels are inversely related to levels of folate, B12, and B6.
- Deficiencies in cystathionine β-synthase increase plasma homocysteine as in homocystinuria and results in premature vascular disease and death due to thrombotic complications before 30 years of age.
- Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.

f) Amino Acids That Form Acetyl CoA or Acetoacetyl CoA

- Phenylalanine and Tyrosine produce acetoacetate during their catabolism.
- Leucine, Isoleucine, Lysine, and Tryptophan form acetyl CoA or acetoacetyl CoA directly, without pyruvate as an intermediate through the pyruvate dehydrogenase reaction.
- Leucine is exclusively ketogenic (acetoacetate and acetyl CoA).
- Isoleucine is both ketogenic and glucogenic (acetyl CoA and succinyl CoA).
- Lysine is exclusively ketogenic (acetoacetyl CoA). Neither of the Lysine's amino groups undergoes transamination as the first step in catabolism.
- Tryptophan is both glucogenic and ketogenic (alanine and acetoacetyl CoA).



❖ <u>Catabolism of Branched Chain Amino Acids:</u>

- Isoleucine, Leucine, and Valine are essential, branch-chained amino acids. The initial steps of their catabolism are similar. Their metabolism occurs primarily by the peripheral tissues (particularly the muscle), rather than by the liver.
- There are three main steps:
  1. **Transamination** by a vitamin B6–requiring enzyme, branched chain amino acid aminotransferase.

2. **Oxidative decarboxylation** by a single multienzyme complex, branched-chain α-keto acid dehydrogenase complex. Notice its decarboxylation NOT deamination!
3. **Dehydrogenation**: Oxidation of the products yields α-β-unsaturated acyl CoA derivatives.

- The End Products:
  1. Isoleucine yields acetyl CoA and succinyl CoA (both ketogenic and glucogenic)
  2. Valine yields succinyl CoA (glucogenic).
  3. Leucine yields acetoacetate and acetyl CoA (ketogenic).
- Coenzymes involved: thiamine pyrophosphate, lipoic acid, FAD, NAD+, and CoA
- Any other details (such as the intermediates) are not included

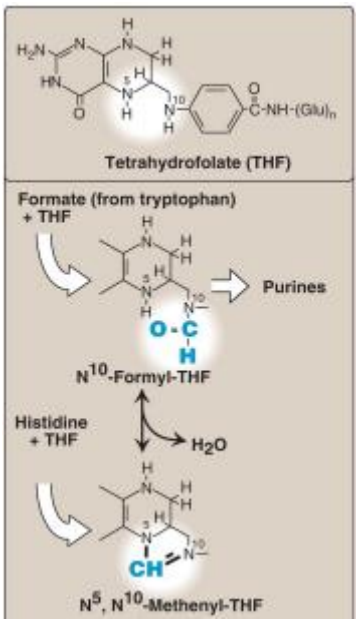
Folic Acid (B9) and Single Carbon Groups

Some synthetic pathways require the addition of single carbon groups. Single carbon groups exist in a variety of oxidation states, including formyl, methenyl, methylene, and methyl. Single carbon groups can be transferred from carrier compounds such as THF and SAM to molecules that are being synthesized. For THF, the carbon unit carried is bound to nitrogen N5, N10, or both. These bound compounds can now be recognized and manipulated by biosynthetic enzymes.

Activation of Folic Acid:

The precursor, inactive form of THF is folic acid. Whether folic acid is ingested from natural (food such as green vegetables) or synthetic (supplements) sources, it is through the inactive form folic acid (or folate). This form can not give or take carbon units.

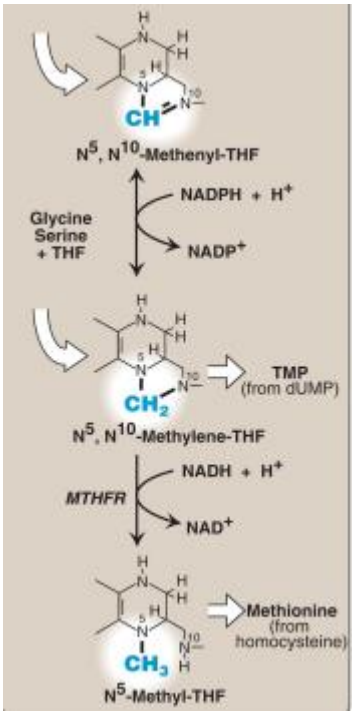
Reduction to tetrahydrofolate occurs through the addition of 4 hydrogens. This is done by **dihydrofolate reductase** in a two step reaction requiring two NADPH.



Interconversions of THF:

- THF begins by carrying a formyl group. This forms N^{10}-Formyl-THF. This compound can be used for the synthesis of purines (nitrogenous bases A+G).
- If a water molecule is lost, a double bond forms, and the single carbon unit is now bound to both N5 and N10. The compound is N^5,N^{10}-Methenyl-THF.

- Reduction of the double bond by NADPH forms a single bond. This makes N^5,N^{10}-Methylene-THF. It is used to make TMP.
- Complete reduction with NADH can occur to break the bond to form N^5-Methyl-THF. This reaction is catalyzed by MTHFR. As seen earlier, N^5-Methyl-THF can be used in the reproduction of methionine.



More on the Enzyme MTHFR:

MHTR is mutated in many individuals in the population. Caucasians have especially high rates of this mutation (up to 50%). With such high rates it's considered a single nucleotide polymorphism (SNP). In Jordan, the percentage of individuals with this mutation is around 20%, with some ethnic groups having higher rates.

This mutation leads to deficiency of MTHFR. This leads to very low synthesis of N^5-Methyl-THF. The amount of deficiency depends on where the mutation occurred. The exact effects of this mutation are unknown. However, the mutation is correlated with many common cancers (breast, lung, and colorectal cancers). Correlation indicates that of the people with these cancers, a higher percentage have this mutation. But remember, correlation does not mean causation! We still do not know if the mutation is a cause of these cancers.

Folic Acid Deficiency and Pregnancy:

Folate deficiency presents as a megaloblastic anemia due to decreased availability of the purines and of the TMP needed for DNA synthesis. Folic acid deficiency is especially dangerous in pregnant women, because it can lead to issues with neuronal development of the fetus, including spina bifida. Some of the fetuses may even die. So, pregnant women must take folic acid for at least the first three months of pregnancy. They should also take it three months before pregnancy, as it increases fertility in females. Currently, folic acid is added to flour and other wheat products to avoid deficiencies in the human population, this process is called folic acid fortification. The issue is, for a pregnant woman in taking all of this extra folic acid, and if she has the MHTFR deficiency, could this possibly be dangerous? If the mutation is a causative agent, this would be very dangerous. Screening of these females should be done, and they should be given N^5-Methyl-THF to protect them from complications that could potentially caused by the mutation (but again, nothing is proven yet).