Sheet Slides

Subject:	Amino Acid Degradation
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Number:	31

After discussing the digestion of proteins to amino acids, the absorption and transport of amino acids, the consequent removal of their nitrogen, and urea synthesis in the previous chapter, we come to the second chapter:

Amino acid degradation and synthesis

Remember: amino acids are classified according to their end-product of catabolism into three groups:

- **Ketogenic** amino acids: Leucine and lysine (both are essential amino acids)
- **Glucogenic and ketogenic** amino acids**:** Isoleucine and the three aromatic amino acids: Tyrosine, Phenylalanine, and Tryptophan (all are essential except for Tyrosine)
- **Glucogenic** amino acids: the rest of essential and nonessential amino acids
- The catabolism of most amino acids produces Krebs cycle intermediates or pyruvate, which means that they can be used in gluconeogenesis (so they are **Glucogenic** amino acids). While few amino acids produce other intermediates that cannot be used to synthesize glucose, like acetoacetate and other compounds and precursors of keto bodies (**Ketogenic** amino acids).

*Amino acids can also be classified by the specific final product to 7 groups, some amino acids might fall into more than one group because it can use different pathways.

1- Amino acids that produce **oxaloacetate: Aspartate and Asparagine**

2- Amino acids that form **α-ketoglutarate via glutamate: Glutamine, Proline, Arginine, Histidine.**

3- Amino acids that form **pyruvate**: **Alanine, Serine, Glycine, Cysteine.**

4- Amino acids that form **fumarate: Phenylalanine and tyrosine**

5- Amino acids that form **Succinyl CoA: Valine, isoleucine, Threonine, Methionine.**

6,7- Amino acids that form **acetyl CoA or acetoacetyl CoA: Leucine, Isoleucine, Lysine, Tryptophan.**

Catabolism of Glycine and Serine:

The smallest amino acid - Glycine - can be cleaved by *Glycine cleavage complex* producing CO_2 and ammonia, reducing NAD^+ to NADH, and forming one carbon moiety - **methylene –** which is carried temporarily on the cofactor tetrahydrofolate **(THF)**.

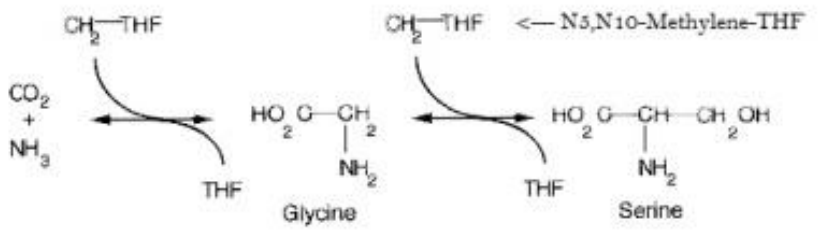
TFH: is a cofactor derived from folic acid, it consists of: pteridine ring, para-aminobenzoic acid (PABA), and couple of glutamate residues. This cofactor is very important for the synthesis of nucleotides and amino acids (women start courses of folic acid administration even before conception to make sure they supply their fetuses with enough levels of THF). Its main function is to transport different carbon moieties, the attachment sites of carbon moieties on THF are nitrogen atoms number 5, number 10, or both together. Methylene – mentioned above – is attached to both N^5 and N^{10}.

Sulfonamides (Sulfa) are bacteriostatic compounds that are similar to PABA in structure, they affect bacterial replication specifically by competing with PABA on the enzyme that synthesizes folic acid, so folic acid won't be formed properly and bacterial cells that lack folic acid won't be able to replicate.

[Minutes: 00-10]

Other examples on THF functions of carrying **carbon moieties**:
- During Tryptophan metabolism, **formyl** is donated to THF, THF then transports it to be used in purine synthesis (Tryptophan produces Alanine and **Niacin**)
- Histidine is a source of **methenyl** (forming N^5,N^{10}-methenyl-THF)
- **Methyl** (carried as N^5-methyl-THF) is used to regenerate methionine from homocysteine.

So Glycine is degraded by the transfer of methylene to THF, and the reaction may go in the reverse direction using N^5,N^{10}-Methylene-THF to produce Glycine, this depends on cellular requirements.
Serine is synthesized by the transfer of methylene from N^5,N^{10}-methylene-THF to Glycine. While the reverse reaction breaks serine to Glycine which continues as mentioned above.



Catabolism of Alanine, Serine, and Cysteine (Amino Acids with 3 carbons):

- Alanine is converted to pyruvate by the transamination reaction carried by *ALT*
- Serine has a catabolic pathway (other than the glycine pathway mentioned above) in which *Serine dehydratase* removes the amino group of serine and produces pyruvate
- Cysteine undergoes desulfurization to produce pyruvate

Catabolism of Threonine:

- Degraded by *Threonine dehydrogenase* to produce aminoacetone
- Or by *Threonine dehydratase* (*Serine dehydratase*) to α-ketobutyrate which is converted to propionyl CoA (then propionyl CoA yields succinyl CoA)

Note: Propionyl CoA is also produced from oxidation of odd-numbered fatty acids.

Catabolism of Aspartate and Asparagine:

- *Asparaginase* hydrolyzes asparagine to aspartate (deamination)
- Aspartate is converted to oxaloacetate by transamination carried by *AST* enzyme

Note: *Asparaginase* is used in treating **leukemia** because leukemic cells require asparagine, so injections of *Asparaginase* will increase degradation of asparagine, thereby lowering plasma levels of asparagine and depriving leukemic cells from it.

Catabolism of amino acids producing α-ketoglutarate (C5 and C6):

Glutamine Glutamate proline arginine histidine

- *Glutaminase* removes an ammonia from Glutamine to produce Glutamate
- Arginine is cleaved by *Arginase* to Ornithine and urea
- Proline is metabolized to Pyrroline-5-carboxylate, then this compound together with ornithine form Gamma semialdehyde glutamate which is then converted to Glutamate
- Glutamate (from diet or from catabolism of amino acids mentioned above)

produces α-ketoglutarate.
- Amino group of Histidine is removed by *Histidase* and the product is Urocanate, which is then converted to 4-imidazolone-5-propionate then produces **FIGlu**, FIGlu is N-Formimino-glutamate.
Note: FIGlu is used to test for THF deficiency, because they usually undergo a reaction in which one carbon moiety is transferred from FIGlu to THF producing N-Formimino-THF and Glutamate. If an accumulation of FIGlu is detected this is an indicator of **folate deficiency**.

[Minutes: 10-20]

Catabolism of some nonpolar amino acid to produce Succinyl CoA:

Methionine, Valine, and Isoleucine all produce Propionyl CoA.
You know that Propionyl CoA undergoes carboxylation D-Methylmalonyl CoA, which is switched to its isomer L-Methylmalonyl CoA. *Mutase* then acts on L-Methylmalonyl CoA and produces Succinyl CoA (this reaction requires B12).
Note: Deficiency in B12 results in academia due to accumulation of L-Methylmalonyl CoA. B12 is also needed in folate metabolism.
* Remember that Threonine also follows Propionyl CoA-Succinyl CoA pathway *

Catabolism of branched-chain amino acids:

	Classification	End product
Leucine	Ketogenic	Acetoacetate and Acetyl CoA
Isoleucine	Glucogenic and Ketogenic	Succinyl CoA and Acetyl CoA
Valine	Glucogenic	Succinyl CoA

One special thing about these amino acids is that they are metabolized mainly in muscles, not in the liver.
Branched-chain amino acids share these reactions in their metabolism pathway:
- Transamination*:* *Branched-chain amino acid aminotransferase* moves the amino group from these amino acids and each one gives its corresponding keto acid
- Oxidative decarboxylation: the multienzyme complex *Branched-chain α-keto acid dehydrogenase (BCKD)* - similar to *Pyruvate dehydrogenase* and *α-*

ketoglutarate dehydrogenase – requires several cofactors: CoA, NAD^+, FAD, TPP, and lipoic acid. When it acts on α-Keto acids it produces their corresponding CoA-derivatives (releasing CO2, oxidizing, and incorporating CoA).

Genetic disorders: some of them are common and testing for them is mandatory in all hospitals, tests are mainly done for newborns and some hospitals test individuals for 20 or even 30 genetic disorder) because these are very serious disorders and can be managed if detected early.
Maple syrup urine disease: it results from defect in *BCKD* which leads to accumulation of αketo acids in the blood, newborns with this disorder show poor feeding, vomiting, and acidosis.

If we didn't detect their disorder early (in the first three weeks) it would affect the brain causing mental retardation, their urine has "a good smell".
Treatment is by restricting the intake of these amino acids throughout the whole life, but they are essential amino acids! so patients should be provided with the least sufficient amount of these amino acids (leucine, isoleucine & valine) and their blood should be monitored (by amino acid analyzer) to major the concentration of these amino acids in it.
Depending on the site of DNA mutation, many isoforms of this disorder can occur; sever, moderate, or mild. One of these forms results from genetic mutation that increases the Km of binding to Thiamine, in this case they found that the patient is Thiamine-responsive (i.e. giving Thiamine to the patient reduces the symptoms).

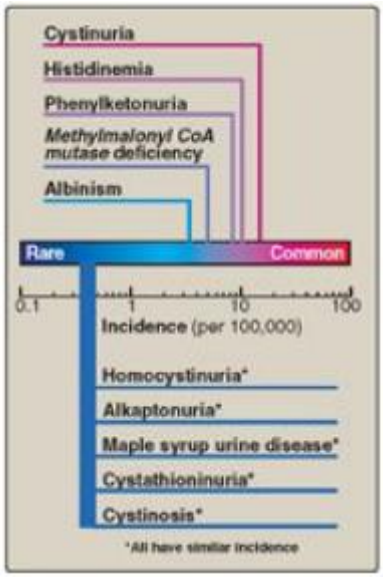


Figure showing the incidence of some disorders, notice that maple syrup urine disease is rare.

* Most of the disorders in the figure will be discussed in the coming lectures *

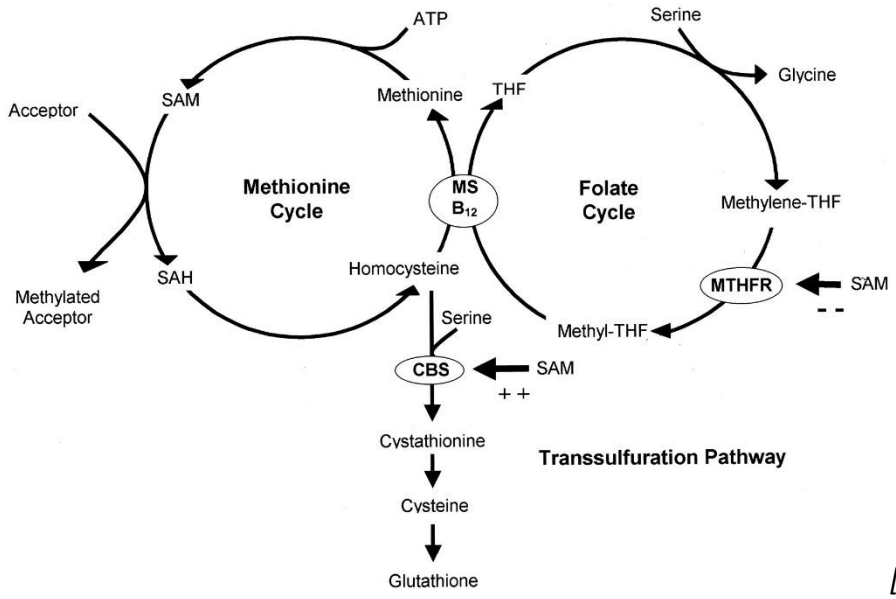
[Minutes: 20-33]

Catabolism of sulfur-containing amino acids: (Methionine and Cysteine)
Methionine is an essential amino acid while Cysteine is not, but if your intake of Methionine is low Cysteine becomes an essential amino acid.
- Methionine (containing thioether) undergoes activation by reacting with ATP, the enzyme that catalyzes this reaction is *Methionine S-adenosyl transferase* producing **S-Adenosyl Methionine (SAM)**, pyrophosphate (which is hydrolyzed), and an inorganic phosphate. SAM is a donor of methyl group and is used in many methylation reactions.

(Bacteria protect their DNA from the invading viruses by methylating it so that nucleotidases won't be able to recognize and degrade bacterial DNA)
When SAM donates a methyl group it becomes s-adenosyl homocysteine (SAH), then adenosine group is hydrolyzed leaving the **homocysteine** (a compound similar to cysteine but with extra [-CH2-] group before the terminal [-SH])
Homocysteine can recycle back to Methionine if the cell needs it, the recycling reaction requires N^5-Methyl-THF (as methyl group donor) and B12 as cofactor, the methyl group is first transferred to the cofactor (B12 or Cobalamin) producing N^5-Methylcobalamin which then transfers the methyl group to Homocysteine.

Note: Another consequence of B12 deficiency is the inability to transfer methyl groups from N^5-Methyl-THF to Homocysteine, which leads to trapping THF in the form of Methyl-THF (and this is the only reaction in which Methyl-THF can participate), so the deficiency in B12 here has an effect similar to folate deficiency and may lead to megaloblastic anemia.

- *Cystathionine synthase* (B6-requring enzyme) acts on Homocysteine and Serine, binding them together to produce Cystathionine, Cystathionine is then cleaved by *Cystathionase* to Cysteine and α-ketobutyrate (that's how Cysteine is produced when the cell needs it and it is nonessential as long as you have enough Methionine to produce it)



[Minutes: 33-43]

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